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HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN For:

Diisopropyl Ether (DIPE)

CAS No. 108-20-3

Prepared by:

ExxonMobil Chemical Company
Shell Chemical LP

For:

American Chemistry Council,
Isopropanol Panel,
Diisopropyl Ether HPV Task Group

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EXECUTIVE SUMMARY

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company and Shell Chemical LP committed thru the Isopropanol Panel, DIPE Task Group of the American Chemistry Council (ACC) to voluntarily compile a Screening Information Data Set (SIDS) that can be used for an initial hazard assessment of diisopropyl ether (DIPE), CAS No. 108-20-3. The data described in this test plan should be used for the purposes of HPV Program and not for regulatory cleanup or criteria development processes.

The assessment includes data for physicochemical, environmental fate, and mammalian and environmental effect endpoints included in the U.S. HPV Program. Additional mammalian data beyond the SIDS endpoints are supplied with this submission.

A literature search identified data for all endpoints under the U.S. EPA HPV Program for DIPE (Table 6); however, the studies for two environmental toxicity endpoints were not sufficiently reliable. All the mammalian toxicity studies in this assessment were assessed as adequate, with reliable data that suggest DIPE generally presents a low order of toxicity for human health. Although data were identified for all aquatic toxicity endpoints, the acute invertebrate and alga toxicity endpoints did not have measured data that were equivalent in quality to the data used to characterize the fish acute toxicity endpoint. Therefore, studies will be conducted to develop measured data that characterize DIPE for these endpoints. The available aquatic toxicity data suggest that DIPE presents a low order of toxicity for the environment.

Results of Mackay Level I distribution modeling at steady state show that DIPE will partition primarily to the air compartment (97.8%), with a negligible amount partitioning to water (2.1%) and soil (0.1%). Level III modeling indicates that at steady state, water is the primary compartment on a percentage basis when the default emission to this compartment is included in the calculations. However, Level III modeling may not be representative of the ultimate disposition of DIPE because default emissions, which use 1000 kg/h/compartment, are not representative of chemical discharge, including to groundwater.

DIPE is volatile, and volatilized DIPE will be quickly degraded in the atmosphere via indirect photodegradation. The DIPE half-life from hydroxyl radical attack is calculated to be approximately 5 hours. Aqueous photolysis and hydrolysis will not contribute to the transformation of DIPE in aquatic environments because it is either poorly or not susceptible to these reactions.

DIPE has a low potential to biodegrade based on results of biodegradation testing. However, a number of published studies in which non-standard guideline methods were used have demonstrated that DIPE is degraded by pure strains and mixed cultures of bacteria when incubated under aerobic conditions. Bioaccumulation of DIPE is unlikely, based on a low bioconcentration factor (bioconcentration factor = 2.95).

Results of testing suggest that DIPE exhibits low aquatic toxicity, based on an analytically measured fish acute toxicity value of 92 mg/L (96-hour LC_{50}) and a nominally measured acute invertebrate toxicity value reported as 190 mg/L (48-hour EC_{50}). Two additional fish acute toxicity studies are available with results that range up

to 900 mg/L for a 24- and 96-hour study. Although there are no reliable measured data for an alga, calculated data are available. Calculated 96-hour EC_{50} and chronic values are 135 and 10 mg/L, respectively.

Available data shows DIPE to be or a low order of acute oral, dermal, and inhalation toxicity with LD_{50} values in excess of 2000 mg/kg and an inhalation LC_{50} >20 mg/kg. High concentrations of DIPE cause CNS depression which is readily reversible on cessation of exposure. DIPE is not a skin irritant but prolonged/repeated contact may cause defatting of the skin, which can lead to dermatitis. The vapours and liquid may be irritating to the eyes at 800 ppm, but not at 500 ppm

There are no reports of human systemic toxicity associated with acute DIPE exposure. DIPE is not expected to be a skin sensitizer. Increased liver weights in rats without histopathology may have been an adaptive effect. There were no adverse effects in repeat dose animal studies other than the male rat kidney effect, which may not be relevant to humans. DIPE does not appear to be a primary reproductive or developmental toxicant. DIPE is not considered to be neurotoxic. DIPE is not genotoxic *in vitro* and is not considered a mutagenic or carcinogenic hazard.

Existing DIPE data for the HPV Program are summarized below. Two studies will be conducted, acute invertebrate and alga toxicity, to provide a consistent and reliable analytically measured data set for the aquatic endpoints.

DIPE Data Availability and Adequacy for Endpoints in the HPV Program

Endpoint	Data Availability	Reference	First Author/ Source	Date
Physical/Chemical Properties				
2.1 Melting Point	Adequate measured	22	Lide *et al.*	1997
2.2 Boiling Point	Adequate measured	22		
2.3 Density	Adequate measured	22		
2.4 Vapor Pressure	Adequate measured	6	Daubert and Danner	1989
2.5 Partition Coefficient	Adequate measured	15	Hansch *et al.*	1995
		8	Eadsforth	1983
2.6 Water Solubility	Adequate measured	12	Gerhartz *et al.*	1987

Endpoint	Data Availability	Reference	First Author/ Source	Date
Environmental Fate				
3.1 Photodegradation (direct and indirect)	Technical discussion (direct)	16	Harris	1982a
		35	Zepp and Cline	1977
	Computer model (indirect)	9	EPI Suite™	2000
3.2 Stability in Water	Technical discussion	13	Gould	1959
		17	Harris	1982b
3.3 Transport between Environmental Compartments (Level I and III)	Computer model	24	Mackay	1998
		25	Mackay *et al.*	1996
3.4 Biodegradation	Adequate measured (Standard Method)	30	Stone and Watkinson	1983
	Additional information (Non Standard Methods)	36 - 46	See Reference Section	-
3.5 Bioaccumulation	Computer model	9	EPI Suite™	2000
Environmental Toxicity				
4.1 Acute/prolonged toxicity to Fish	Adequate measured	3	Broderius and Kahl	1985
	Adequate measured	11	Geiger *et al.*	1986
	Adequate measured	33	Veith *et al.*	1983
	Computer model	10	ECOSAR	2004
	Measured (not reliable)	2	Bridié *et al.*	1979
	Measured (not reliable)	7	Dawson	1975/77

Endpoint		Data Availability	Reference	First Author/ Source	Date
Environmental Toxicity					
4.2 Acute Toxicity to Aquatic Invertebrates		Measured (nominal) Testing Proposed	29	Stephenson	1983
		Computer model	10	ECOSAR	2004
4.3 Toxicity to Aquatic Plants		Measured (not reliable) Testing Proposed	29	Stephenson	1983
		Computer model	10	ECOSAR	2004
Mammalian Toxicity					
5.1.1. Acute Oral Toxicity		Adequate measured	20	Kimura *et al.*	1971
			23	Machle *et al.*	1939
5.1.2 Acute Inhalation Toxicity		Adequate measured	23		
5.1.3 Acute Dermal Toxicity		Adequate measured	23		
5.2 Sensitization		Adequate measured	34	Wass and Belin	1990
5.3 Repeated Dose Toxicity		Adequate measured	5	Dalbey and Feuston	1996
			27	Rodriguez and Dalbey	1997
5.4 Genetic Toxicity In Vitro	Bacterial mutagenicity	Adequate measured	4	Brooks *et al.*	1998
	Chromosomal damage				
5.5 Developmental Toxicity/Teratogenicity		Adequate measured	5	Dalbey and Feuston	1996
5.6 Additional Information – Sensory Irritation in Humans		Adequate measured	18	Hine *et al.*	1955
			28	Silverman *et al.*	1946

TABLE OF CONTENTS

TEST PLAN FOR DIISOPROPYL ETHER (CAS No. 108-20-3)

I. INTRODUCTION

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company and Shell Chemical LP committed thru the Isopropanol Panel, DIPE Task Group of the American Chemistry Council (ACC) to voluntarily compile a Screening Information Data Set (SIDS) that can be used for an initial hazard assessment of diisopropyl ether (DIPE), CAS No. 108-20-3. The data described in this test plan should be used for the purposes of HPV Program and not for regulatory cleanup or criteria development processes.

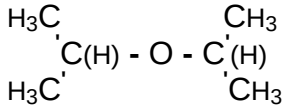
The assessment includes data for selected physicochemical, environmental fate, and mammalian and environmental effect endpoints required by the U.S. HPV Program. Additional data beyond the SIDS endpoints (irritation, sensitization, and neurotoxicity) are supplied with this submission.

Procedures to assess the reliability of selected data for inclusion in this test plan were based on guidelines described by Klimisch *et al*. (1997) and identified within the U.S. EPA (1999a) document titled *Determining the Adequacy of Existing Data*. The following sections describe DIPE and its manufacturing process, and data used to characterize the various endpoints in the HPV Program. Additional mammalian data beyond SIDS requirements are also provided together with exposure information that allow for further assessment of data completeness. After a review of the existing data, the sponsors believe that reliable and consistent data have been identified that can characterize all but two SIDS endpoints. Two studies will be conducted, acute invertebrate and alga toxicity, to provide a consistent and reliable measured data set for the environmental endpoints.

II. CHEMICAL DESCRIPTION, MANUFACTURING PROCESS, USE, AND EXPOSURE

DIPE is a small molecular weight ether represented with the following chemical formula and structures:

$C_6H_{14}O$ $(CH_3)_2CHOCH(CH_3)_2$



DIPE is manufactured by a series of chemical reactions as a co-product in the synthesis of isopropyl alcohol (IPA), typically including a propane feedstock and water to produce a high purity product. In a first reaction zone the propane in a feedstock (after removal of hydrocarbons containing four or more carbon atoms from the feedstock via fractionation) is dehydrogenated in the presence of a dehydrogenation catalyst to form propylene. After removing hydrogen, the propane and propylene mixture generated in the first reaction zone is separated into propane-enriched and propylene-enriched streams. The propylene-enriched stream contains at least 65% (wt.) propylene. The propane-enriched stream is recycled to the feedstock fractionation unit, and the propylene in the propylene-enriched stream is reacted with water in a second reaction zone in the presence of an acidic catalyst to form IPA; some of this can concurrently react with propylene to produce diisopropyl ether. A portion of the second reaction zone

effluent is recycled to the second reaction zone, and the remainder may be collected or further separated to provide a high purity diisopropyl ether product.

DIPE can be used as a gasoline blending component. Other uses are as a solvent for animal, vegetable, and mineral oils. It is also used as an extraction solvent for dewaxing of paraffin-based oil products. DIPE can be used as a solvent in medicine production and paint cleaning.

Because DIPE is volatile, inhalation is expected to be the major route of human exposure and ingestion a minor route. While the HPV Program is a hazard data collection effort and does not require evaluation of potential environmental impacts to groundwater, this may be a consideration for DIPE within a risk assessment framework. DIPE has been found in groundwater and drinking water wells within the U.S. Odor and taste studies indicate that DIPE has a very low odor threshold (< 10ppb). DIPE in drinking water may affect the use of drinking water. To the extent that DIPE may impact the use of surface or groundwater, appropriate assessment and remediation (if necessary) should be implemented.

III. TEST PLAN RATIONALE AND DATA SUMMARY

All DIPE test data identified within this document were developed using the parent substance. The data used to characterize the alga endpoints were developed using the ECOSAR computer model (ECOSAR, 2004) provided within EPI Suite™ (2000). This model applies an equation for neutral organics to estimate aquatic toxicity and is therefore considered appropriate to estimate aquatic toxicity for DIPE. As further justification, calculated data from this model for the fish and daphnid effect endpoints are consistent with the measured data for these organism types, supporting its use to provide adequate data for the alga endpoints.

Data used to characterize the various physicochemical, environmental fate, and environmental and mammalian health endpoints are described below.

A. Physicochemical Data

Measured DIPE physicochemical data from the literature are listed in Table 1. The log K_{ow} value referenced as Hansch *et al.* (1995) was selected over the value referenced by Eadsforth (1983), because the primary reference cited in Hansch *et al.* (1995) has been published in external peer reviewed literature, has been carefully critiqued and included in the Syracuse Research Corp., EPISUITE® data base. That value, because of its' inclusion has been widely used and is commonly accepted. The Eadsforth (1983) reference is an internal Shell Research publication with no external review.

Table 1. Select Physico-Chemical Properties for DIPE.

MELTING POINT (ºC)	BOILING POINT (ºC at 1013 hPa)	DENSITY (g/cm^3 at 20°C)	VAPOR PRESSURE (Pa at 25°C)	WATER SOLUBILITY (mg/L at 20°C)	LOG K_{ow} (25°C)
-86.8 (Lide *et al*., 1997-1998)	68.5 (Lide *et al*., 1997-1998)	0.7241 (Lide *et al*., 1997-1998)	19,865 (Daubert and Danner, 1989)	8,800 (Gerhartz *et al*., 1987)	1.52 (Hansch *et al*., 1995) 2.4 Eadsforth, 1983)

B. Environmental Fate Data

Biodegradation - Standard Guideline Results Under Aerobic Conditions

Biodegradation of an organic substance by bacteria can provide energy and carbon for microbial growth. This process results in a structural change of an organic substance and can lead to the complete degradation of that substance, producing carbon dioxide and water.

The test guideline used to assess the biodegradability of DIPE was OECD 301D, Closed Bottle Biodegradation Test. This test system design uses a sealed bottle, which is appropriate considering the test material is relatively volatile. The source of the microbial inoculum used in this study was a domestic wastewater treatment facility and the inoculum was not acclimated.

DIPE did not exhibit measurable biodegradation (0%) after 28 days under the conditions of this test design (Stone and Watkinson, 1983). While these data indicate a reduced ability for DIPE to biodegrade in compartments such as soil, water, sediment, and groundwater, there are other data in the open literature which indicate that DIPE can biodegrade in the environment. A biodegradation inhibition study was also included in the test design and it showed that the test substance did not inhibit the biodegradability of the positive control substance, sodium benzoate.

Biodegradation - Non Standard Guideline Results Under Aerobic and Anaerobic Conditions

Diisopropyl ether (DIPE) is one of a group of similar compounds referred to as alkyl ether oxygenates (AEO) that are added to reformulated gasoline. Biodegradation studies with DIPE and other AEO compounds have demonstrated the ability of these substances to be consumed by pure strains and mixed cultures of bacteria when incubated under aerobic conditions. Church and Tratnyek (2000) showed that bacterial strain PM1, which had been acclimated to methyl t-butyl ether (MTBE), could mineralize MTBE and demonstrated similar degradation rates for DIPE and other AEOs. They concluded that similar enzymes were responsible for all the degradation reactions. Additional evidence showing the wide spectrum of activity of the bacterial enzyme systems to degrade AEOs was provided by Hernandez-Perez *et al.* (2001). Using

isolated *Gordonia terrae* (strain IFP 2001) that had been grown on ethyl t-butyl ether (ETBE), degradation of a variety of other AEOs could be achieved. DIPE was degraded 78% within 24 hours in their study (Hernandez-Perez *et al.,* 2001).

Optimum biodegradation in mixed culture systems occurred when the microbial culture is allowed a period of acclimation to the substrate. For example, Bridié *et al.* (1979) measured only 7% consumption of the theoretical oxygen demand when DIPE was tested in a 5-day BOD test. In contrast, Cano *et al.* (1999) showed rapid utilization of DIPE when activated sludge was conditioned to a cocktail of volatile organic compounds for two months. In a continuous flow reactor, DIPE removal averaged 99.4%. Cano *et al.* (1999) also measured high rates of biodegradation of DIPE when comparing the continuous treatment method (EPA Method 304B) (EPA, 1994) to two batch treatment methods (BOX and SBT methods; Rajagopalan *et al.,* 1998). Based on the measured rate constants, the authors considered DIPE to be readily biodegradable. Pruden *et al.* (2001) also observed high removal rates (e.g., 99.9%) of DIPE through a continuous flow reactor system. The performance of the reactors was enhanced when biomass was retained in the reactor, suggesting that a long biomass residence time may be needed for complete mineralization.

Biodegradation of DIPE is not always observed in biodegradation assays. Zenker *et al.* (1999) failed to show biodegradation of DIPE over a 1-year period using indigenous microflora in sediment and water from an aquifer that had been previously exposed to MTBE. Given the apparent need of microbial communities for a period of acclimation to DIPE, it is unlikely that DIPE would be considered readily biodegradable in standard guideline studies. However, the evidence shows that DIPE can be inherently degraded by pure strains of bacteria and mixed enrichments of activated sludge microorganisms.

While available research shows that DIPE is capable of being biodegraded under aerobic conditions, anaerobic biodegradation is extremely difficult and this substance is considered recalcitrant under those conditions. Suflita *et al.* (1993) showed no biodegradation of DIPE after 252 days of anaerobic incubation. Substrate was added as 50 ppm carbon to sediment and groundwater collected from a methanogenic portion of a shallow anoxic aquifer. Similarly, DIPE was evaluated for anaerobic biodegradability under methanogenic conditions as well as sulfate and nitrate-reducing conditions (Mormile *et al.,* 1994). Inocula from three sources (e.g., sediment/groundwater from an aquifer impacted by landfill leachate, sediment/surface water from a river impacted by oil storage, and sediment/surface water from a creek impacted by industrial waste and domestic sewage) were used in separate incubations to assess anaerobic biodegradation in sealed serum bottles. No DIPE biodegradation was measured over incubation periods of 85 days (nitrate-reducing conditions), 180 days (methanogenic conditions), and 244 days (sulfate-reducing conditions). Lack of methane production reported by Suflita and Mormille (1993) does not preclude partial anaerobic biodegradation of DIPE in their studies because only methane was monitored. They found evidence in the form of methane and carbon dioxide production to conclude that anaerobic biodegradation was occurring, although the authors stated that anaerobic biodegradation was not a widespread phenomena and extremely difficult for these compounds.

Photodegradation - Photolysis

Direct photochemical degradation occurs through the absorbance of solar radiation by a

chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer (Harris, 1982a).

An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). The oxygen non-bonding electrons in ethers do not give rise to absorption above 160 nm, which is why pure ether solvents can be used in spectroscopic studies. Consequently, DIPE is not subject to photolytic processes in the aqueous environment.

Photodegradation - Atmospheric Oxidation

Photodegradation can be measured (US EPA, 1999a) or estimated using an atmospheric oxidation potential (AOP) model accepted by the EPA (US EPA, 1999b). Atmospheric oxidation as a result of hydroxyl radical attack is not direct photochemical degradation, but rather indirect degradation.

DIPE has the potential to volatilize to air, based on a vapor pressure of 19,865 Pa at 25°C (Daubert and Danner, 1989), where it is subject to atmospheric oxidation. In air, DIPE can react with photosensitized oxygen in the form of hydroxyl radicals (OH-). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPI Suite™, 2000) calculates a chemical half-life for a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated), based on an OH- reaction rate constant and a defined OH- concentration.

DIPE has a calculated half-life in air of 5.3 hours or 0.4 days (12-hour day), based on a rate constant of 24.34×10^{-12} cm^3/molecule*sec and an OH- concentration of 1.5×10^6 OH-/cm^3.

Stability in Water (Hydrolysis)

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with leaving groups that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Gould, 1959). The lack of a suitable leaving group renders a compound resistant to hydrolysis. DIPE is resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive and Harris (1982b) identifies ether groups as generally resistant to hydrolysis. Therefore, hydrolysis will not contribute to the removal of DIPE from the environment.

Chemical Distribution In The Environment (Fugacity Modeling)

Fugacity-based multimedia modeling provides basic information on the relative distribution of a chemical between selected environmental compartments (i.e., air, soil, water, sediment, suspended sediment, and biota). Two widely used fugacity models are the EQC (Equilibrium Criterion) Level I and Level III model (Mackay, 1996; Mackay,

1998). The Mackay Level I and Level III Models do not include a groundwater compartment.

The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as percent of chemical partitioned to 6 compartments (air, soil, water, suspended sediment, sediment, biota) within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical may to partition, based on selected physical parameters. The Level III model uses the same physical parameters as the Level I model, but also requires half-life degradation data for the air, soil, water, and sediment compartments, as well as emission parameters for the air, water, and soil compartments.

Results of the Mackay Level I environmental distribution model (Table 2) suggest that DIPE will partition primarily to the air, >97%. These results can be largely explained by its vapor pressure, 19,865 Pa at 25°C (Daubert and Danner, 1989). In comparison, the Level III model suggests that the majority of DIPE will partition to the water compartment, 61%, followed by the air and soil compartments with approximately equal partitioning (Table 3). These results can be explained by the model parameters, including the use of default emission rates and degradation half-lives.

Table 2. Environmental distribution as calculated by the Mackay (1998) Level I fugacity model.

ENVIRONMENTAL COMPARTMENT	DIPE DISTRIBUTION* (%)
Air	97.83
Water	2.10
Soil	0.06
Sediment	<0.01
Suspended Sediment	<0.01
Biota	<0.01

*Distribution is based on the following model input parameters for DIPE:

Molecular Weight	102.18
Temperature	25° C
Log K_{ow}	1.52
Water Solubility	8,800 g/m^3
Vapor Pressure	19,865 Pa
Melting Point	-86.8° C

Table 3. Environmental distribution as calculated by the Mackay (1998) Level III fugacity model.

ENVIRONMENTAL COMPARTMENT	DIPE DISTRIBUTION* (%)
Air	19.40
Water	61.00
Soil	19.50
Sediment	0.10

*Distribution is based on the following model input parameters for DIPE:

Emission Rate of 1,000 kg/hr into each of the air, water, and soil compartments

Molecular Weight	102.18
Temperature	25° C
Log K_{ow}	1.52
Water Solubility	8,800 g/m^3
Vapor Pressure	19,865 Pa
Melting Point	-86.8° C

Bioaccumulation Potential

A bioconcentration factor (BCF) of 2.95 (log BCF = 0.47) for DIPE is calculated (EPI Suite^{TM}, 2000) using a log K_{ow} value of 1.52 (Hansch *et al*., 1995). A BCF of 14.06 (log BCF = 1.15) is calculated (EPI Suite^{TM}, 2000) when a log K_{ow} value of 2.4 (Eadsforth, 1983) is used. These data indicate that DIPE has a low BCF and is not expected to bioaccumulate.

C. Aquatic Toxicity Data

Data are available to characterize the fish toxicity of DIPE. Based on measured test concentrations, 96-hour LC_{50} toxicity values of 91.7 to 900 mg/L have been reported (Broderius and Kahl, 1985; Geiger *et al.*, 1985; Veith *et al.*, 1983). Fathead minnows (*Pimephales promelas*) were exposed to DIPE in a 96-hour flow-through experiment resulting in an LC_{50} of 900 mg/L (Broderius and Kahl, 1985). Geiger *et al.* (1985) also evaluated the toxicity of DIPE to *P. promelas* in flow-through exposures and reported a 96-hour LC_{50} of 476 mg/L. These values are considerably higher than the 96-hour LC_{50} of 91.7 mg/L measured by Veith *et al.* (1983) in flow through exposures with *P. promelas*. Dawson *et al.* (1977) conducted static 96-hour experiments using *Lepomis macrochirus* and the saltwater species *Menidia beryllina*. The LC_{50} values measured in these experiments were 7000 and 6600 mg/L, respectively. The test with *L. macrochirus* did not yield a monotonic increasing concentration-response and the data reported by Dawson *et al.* are not considered reliable. Bridié *et al.* (1979) measured a 24-hour LC_{50} of 380 mg/L for the goldfish *Carassius auratus* exposed to DIPE under static conditions. However, the report lacked sufficient detail to assess study quality and determine whether the results were based on nominal or measured values.

The acute fish data are adequate for the HPV Program and range from 91 to 900 mg/L. There is also an ECOSAR (2004) calculated fish 96-hour LC_{50} of 215 mg/L, which is within the reported range of acute toxicity. This model is appropriate to estimate aquatic toxicity for this class of chemicals.

Stephenson (1983) reported a 48-hour invertebrate (*Daphnia magna*) EC_{50} toxicity value of 190.0 mg/L based on nominal test concentrations. A 48-hour daphnid LC_{50} toxicity value of 220 mg/L was estimated using the ECOSAR (2004) model.

There are no reliable measured algal toxicity data. Stephenson (1983) conducted an algal study and reported a 96h EC_{50} of >1000 mg/L. Test concentrations were not measured and there is no indication in the report whether the test vessels were sealed. The reported LC_{50} value may reflect a loss of test substance by volatilization if the flasks were not tightly sealed. A green alga 96-hour EC_{50} toxicity value of 135 mg/L and a 96-hour chronic value of 10.2 mg/L were calculated (ECOSAR, 2004).

Conclusion

Based on the available data, DIPE presents a low order of acute toxicity to aquatic species. Although the reported invertebrate study was assessed as reliable, the results are based on nominal values. Therefore, an additional study will be conducted that is comparable in quality to the fish studies based on measured results. Although a study was reported for an alga species, it was assessed as unreliable. Therefore, an alga study will be conducted that reports measured results.

Table 4. Aquatic Toxicity Values for DIPE.

ENDPOINT	MEASURED VALUE(S) (mg/L)	CALCULATED VALUE (mg/L)
Fish 96-hr LC_{50}	91.7 (Veith, 1983) to 900 (Broderius and Kahl, 1985)	214.1 (ECOSAR, 2004)
Daphnid 48-hr EC_{50}/LC_{50}	190.0* (Stephenson, 1983)	221.9 (ECOSAR, 2004)
Alga 96-hr EC_{50}	No reliable measured data	134.9 (ECOSAR, 2004)
Alga 96-hr ChV	No reliable measured data	10.2 (ECOSAR, 2004)

* nominal value

D. Human Health Effects Data

Mammalian toxicity data for DIPE are summarized below in Table 5. Each endpoint is discussed in the following sections. Additional data for studies beyond those required in the HPV Program are also presented below.

Acute Toxicity

DIPE is low in acute toxicity to mammals. Single lethal dosages/concentrations of DIPE to laboratory animals range from 4.5 to 16.5 g/kg (LD_{50}) for oral exposure, greater than 20 mL/kg (LD_{50}) for dermal exposure and between 8000 and 16000 ppm (33.6 and 67.2 mg/L) for inhalation exposure (Kimura *et al*., 1971). Typical clinical signs in acutely poisoned animals are the result of central nervous system (CNS) effects and include spasmodic movement, tremors, convulsions, incoordination and unsteadiness, narcosis, anesthesia, coma and respiratory depression (Machle *et al.,* 1939). At necropsy,

lesions in affected animals following acute exposure include gastrointestinal irritation, visceral congestion and pulmonary edema (Machle *et al*., 1939).

There are no reports of human systemic toxicity associated with acute DIPE exposure.

Conclusion

DIPE is of a low order of acute oral, dermal, and inhalation toxicity with LD_{50} values in excess of 2000 mg/kg and an inhalation LC_{50} >20 mg/kg.

Genotoxicity

In vitro

DIPE is not genotoxic in a number of *in vitro* assays. DIPE did not induce reverse gene mutation in bacterial tester strains S. *typhimurium* (6 strains), and *E. coli* (3 strains) or mitotic gene conversion in the yeast *S. cervisiae* JD1, with or without metabolic activation. DIPE did not induce chromosome damage in cultured rat liver $(RL_4)_{or}$ CHO cells (Brooks *et al,* 1988).

Conclusion

DIPE is not genotoxic *in vitro* and DIPE is not considered a mutagenic hazard.

Repeated Dose Toxicity

A number of subchronic inhalation studies exist for DIPE. Rats were exposed to 0, 480, 3300, and 7100 ppm DIPE for 6 hours/day, 5 days/wk for 13 weeks. Increases in liver and kidney weights were seen at 3300 and 7100 ppm in both males and females. Some evidence of increased incidence of hyaline droplets in kidney proximal tubules was observed in high dose males only. No effects on serum chemistry, hematology, or pathology were noted at any dose level. The no observed adverse effect level (NOAEL) for this study was 480 ppm (Dalbey and Feuston, 1996).

Guinea pigs, rabbits and monkeys were subchronically exposed to DIPE under the following conditions: 0.1% (1000 ppm) for 3 hours/day, 0.3% (3000 ppm) for 2 hours/day, or 1.0% (10000 ppm) for 1 hour/day for 20 exposures. In addition, rabbits and monkeys received 3.0% (30000 ppm) for 10 exposures. No major deleterious effects were noted in any animals. Some CNS depression was seen in monkeys at 1% and guinea pigs at 3.0% DIPE. Anesthesia with a prompt recovery upon cessation of exposure and some body weight loss were seen at 3% in monkeys (Machle *et al.,* 1939).

Reproductive and Developmental Toxicity

Rats were administered 0, 430, 3095, and 6745 ppm DIPE for 6 hours/day on gestations days 6-15. Maternal effects at the high dose included increased salivation and lacrimation during and immediately following exposure. A slight decrease in food consumption was noted at 3095 and 6745 ppm. A concentration-related increase in the incidence of rudimentary ribs was observed (statistically significant at 3095 and 6745 ppm), but the significance of this finding is not known. The NOAEL for both maternal and developmental effects under conditions of this study was 430 ppm (Dalbey and Feuston, 1996).

No changes in reproductive organ weights and structure or sperm and spermatid number at any dose group were noted in rats exposed to 0, 480, 3300, and 7100 ppm DIPE for 6 hours/day, 5 days/wk for 13 weeks (Dalbey and Feuston, 1996).

Conclusion

NOAEL for both maternal and developmental effects in the developmental study was 430 ppm and the NOAEL for the subchronic study was 480 ppm.

Additional Human Health Effects Data

Irritation

DIPE is mildly irritating to skin, eye and respiratory mucosa in limited animal studies. Single or repeated exposures of DIPE to rabbit skin produced some reddening and dermatitis that subsided after 2 weeks. Direct application to rabbit eyes produces trace effects (Machle *et al*., 1939).

Irritation effects associated with DIPE vapor have been reported in human volunteers. Silverman *et al*. (1946) reported that 35% of humans exposed to DIPE vapor at a concentration of 300 ppm objected to the unpleasant odor of the solvent. At 800 ppm for 5 minutes, most subjects reported irritation of the eyes and nose, and the most sensitive reported respiratory discomfort. Concentrations above 1000 ppm DIPE resulted in complaints of strong irritation to the eyes and respiratory tract. Another study evaluated 5-minute exposures in volunteers and found only slight irritation of the nose at 400 ppm progressing to slight irritation of nose, eyes and respiratory tract at 800 ppm (Hine *et al*., 1955). Subjective reporting and the potential influence of odor complicate interpretation of these studies.

Conclusion

DIPE is not a skin irritant but prolonged/repeated contact may cause defatting of the skin, which can lead to dermatitis. The vapours and liquid may be irritating to the eyes at 800 ppm, but not at 300 ppm.

Sensitization

No *in vivo* skin sensitization studies are available for DIPE. A mathematical model for predicting sensitization based on chemical reactivity suggests a lack of sensitization potential for DIPE (Wass and Belin, 1990).

Conclusion

DIPE is not expected to be a skin sensitizer.

Neurotoxicity

Subchronic neurotoxicity potential was evaluated in rats exposed to 0, 450, 3250, or 7060 ppm DIPE by inhalation for 5 days/wk for 13 weeks. Functional observational battery (FOB) and motor activity was determined at 0, 4, 8, and 13 weeks. Minor decreases in FOB activity at 450 and 7060 ppm and in figure eight motor activity at 7060 ppm were noted at week 4. Some increases in figure eight motor activity were observed in the 450 ppm group at week 4. These changes were not seen at later time points and other FOB parameters and clinical signs were unaffected by treatment. No alterations were noted in microscopic examination of brain, spinal cord, dorsal root ganglia, and sciatic nerve (Rodriguez and Dalbey, 1997).

Conclusion

Inhalation exposures to DIPE at concentrations as high as 7060 ppm for 13 weeks resulted in few observable effects on the nervous system.

Carcinogenicity

DIPE was assessed in a long term gavage study in rats at dose levels of 0, 250 and 1000 mg/kg/day, 4 days a week for 78 weeks (Belpoggi et al, 2002; no robust summary provided). There were a number of deficiencies in design and reporting of this non-conventional study, which made interpretation difficult. These included the maintenance of the animals to their natural death (usually studies are terminated at the end of a predetermined exposure period and/or survival level), lack of detail in reporting statistical significance of tumor incidence (e.g., combined lymphoma and leukemia), and limited reporting of survival. There was no indication of or comparison to historical control data. For these reasons the findings and the significance of such are questionable and are considered equivocal.

All animals were observed until spontaneous death and the experiment ended after 163 weeks. There were no significant differences between treated and control groups in daily food or water consumption, body weight, behavior or non-neoplastic pathological changes. Survival was decreased in treated males compared to controls between the 56^{th} and 88^{th} weeks of age. A statistically significant increase in total malignant tumours was reported in males at the low dose only and a significant trend in females of both treated groups. The incidence of carcinomas of the ear duct in males was statistically significant but was not dose related. A statistically significant increase in combined hemo/lympho-reticular neoplasias (% tumor-bearing animals) was seen in males and females at both dose levels. The increase in tumor incidence was not statistically significant for low dose males but the trend was. Significance was not reported for individual tumours (% tumor bearing animals) or for individual types of lymphoma or leukemia.

Conclusion

The findings of this “lifetime” carcinogenicity study in rats are equivocal.

Table 5. Mammalian Toxicity Endpoint Summary for DIPE.

TOXICITY ENDPOINT		RESULTS	REFERENCE
Acute	Inhalation	Low toxicity	Kimura *et al*., 1971; Machle *et al.,* 1939
	Oral	Low toxicity	Kimura *et al*., 1971; Machle *et al.,* 1939
	Dermal	Low toxicity	Kimura *et al*., 1971; Machle *et al.,* 1939
Irritation	Skin	Minimal irritant	Machle *et al*., 1939
	Eye	Minimal irritant	Machle *et al*., 1939
	Respiratory	Sensory irritant	Hine *et al*., 1955; Silverman *et al*., 1946
Sensitization		Negative *in vitro* sensitizer	Wass and Belin, 1990
Repeated Dose		Liver and kidney effects	Dalbey and Feuston, 1996
Reproductive		No effects on reproductive organ structure or sperm/spermatid number.	Dalbey and Feuston, 1996
Developmental		Equivocal developmental effect at maternal effect level	Dalbey and Feuston, 1996
Neurotoxicity		Minor reversible effect on CNS	Rodriguez and Dalbey, 1997
Genotoxicity	*In vitro* mutation	Negative	Brooks *et al*., 1988
	In vitro chromosome aberration	Negative	Brooks *et al*., 1988

V. TEST PLAN SUMMARY

A search for existing studies/information identified data to characterize all endpoints under the U.S. EPA HPV Program for DIPE (Table 6). However, the acute invertebrate and alga toxicity endpoints did not have measured data that were equivalent in quality to the data used to characterize the fish acute toxicity endpoint. Therefore, studies will be conducted to develop new data for these endpoints. A dossier containing the robust summaries of the data presented in this test plan is provided in the Appendix.

Table 6. DIPE Data Availability and Adequacy for Endpoints in the HPV Program.

Endpoint	Data Availability	Reference	First Author/ Source	Date
Physical/Chemical Properties				
2.1 Melting Point	Adequate measured	22	Lide *et al.*	1997
2.2 Boiling Point	Adequate measured	22		
2.3 Density	Adequate measured	22		
2.4 Vapor Pressure	Adequate measured	6	Daubert and Danner	1989
2.5 Partition Coefficient	Adequate measured	15	Hansch *et al.*	1995
		8	Eadsforth	1983
2.6 Water Solubility	Adequate measured	12	Gerhartz *et al.*	1987

Endpoint	Data Availability	Reference	First Author/ Source	Date
Environmental Fate				
3.1 Photodegradation (direct and indirect)	Technical discussion (direct)	16	Harris	1982a
		35	Zepp and Cline	1977
	Computer model (indirect)	9	EPI Suite™	2000
3.2 Stability in Water	Technical discussion	13	Gould	1959
		17	Harris	1982b
3.3 Transport between Environmental Compartments (Level I and III)	Computer model	24	Mackay	1998
		25	Mackay *et al.*	1996
3.4 Biodegradation	Adequate measured (Standard Method)	30	Stone and Watkinson	1983
	Additional information (Non Standard Methods)	36 - 46	See Reference Section	-
3.5 Bioaccumulation	Computer model	9	EPI Suite™	2000

Endpoint	Data Availability	Reference	First Author/ Source	Date
Environmental Toxicity				
4.1 Acute/prolonged toxicity to Fish	Adequate measured	3	Broderius and Kahl	1985
	Adequate measured	11	Geiger *et al.*	1986
	Adequate measured	33	Veith *et al.*	1983
	Computer model	10	ECOSAR	2004
	Measured (not reliable)	2	Bridié *et al.*	1979
	Measured (not reliable)	7	Dawson	1975/77
4.2 Acute Toxicity to Aquatic Invertebrates	Measured (nominal) Testing Proposed	29	Stephenson	1983
	Computer model	10	ECOSAR	2004
4.3 Toxicity to Aquatic Plants	Measured (not reliable) Testing Proposed	29	Stephenson	1983
	Computer model	10	ECOSAR	2004

Endpoint		Data Availability	Reference	First Author/ Source	Date
Mammalian Toxicity					
5.1.1. Acute Oral Toxicity		Adequate measured	20	Kimura *et al.*	1971
			23	Machle *et al.*	1939
5.1.2 Acute Inhalation Toxicity		Adequate measured	23		
5.1.3 Acute Dermal Toxicity		Adequate measured	23		
5.2 Sensitization		Adequate measured	34	Wass and Belin	1990
5.3 Repeated Dose Toxicity		Adequate measured	5	Dalbey and Feuston	1996
			27	Rodriguez and Dalbey	1997
5.4 Genetic Toxicity In Vitro	Bacterial mutagenicity	Adequate measured	4	Brooks *et al.*	1998
	Chromosomal damage				
5.5 Developmental Toxicity/Teratogenicity		Adequate measured	5	Dalbey and Feuston	1996
5.6 Additional Information – Sensory Irritation in Humans		Adequate measured	18	Hine *et al.*	1955
			28	Silverman *et al.*	1946

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APPENDIX

Data Dossier (Robust Study Summaries) for Diisopropyl Ether (CAS No. 108-20-3)

(The format of the following dossier is taken largely from IUCLID, International Uniform Chemical Information Database)

Data Dossier (Robust Study Summaries) for Diisopropyl Ether (CAS No. 108-20-3)

1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	organic
Physical status	:	liquid
Purity	:	
Color	:	
Odor	:	

1.2 SYNONYMS AND TRADENAMES

2,2'-Oxybis-propane

2,2'-Oxybispropane

Propane, 2,2'-oxybis-

2-Isopropoxy propane

2-Isopropoxypropan

2-Isopropoxypropane

Dipropyloxid

IPE

DIPE

Isopropyl ether

Isopropylether

Diisopropyl ether

Diisopropylether

2.1 MELTING POINT

Value	:	= -86.8 °C
Method	:	other: not specified
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS # 108-20-3)
Test substance	:	CAS No. 108-20-3; diisopropylether; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint
Reference Number		(14)

2.2 BOILING POINT

Value	:	= 68.5 °C at 1013 hPa
Method	:	other: not specified
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS # 108-20-3)
Test substance	:	CAS No. 108-20-3; diisopropylether; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint
Reference Number		(14)

2.3 DENSITY

Type	:	density
Value	:	= .7241 g/cm³ at 20 °C
Method	:	other: not specified
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS # 108-20-3)
Test substance	:	CAS No. 108-20-3; diisopropylether; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint
Reference Number		(14)

2.4 VAPOUR PRESSURE

Value	:	= 198.65 hPa at 25 °C
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS # 108-20-3)
Method	:	Method not specified.
Test substance	:	CAS No. 108-20-3; diisopropylether; purity is unknown.
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data were not reviewed for quality, however, the reference is from a peer-reviewed

handbook.

Flag : Critical study for SIDS endpoint
Reference Number (4)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 1.52 at 25 °C
Method : other (measured)
GLP : no data
Test substance : Diisopropyl ether (CAS # 108-20-3)
Method : Method not specified.
Test substance : CAS No. 108-20-3; diisopropylether purity is unknown.
Reliability : (2) valid with restrictions
The value cited by the authors is a measured and preferred value. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag : Critical study for SIDS endpoint
Reference Number (10)

Partition coefficient : octanol-water
Log pow : = 2.4 at °C
Method : other
GLP : No
Test substance : Diisopropyl ether (CAS No. 108-20-3)
Method : Indirect method by reverse-phase HPLC
Result : Log Pow = 2.4 (Pow = 250) at pH 6.7
Test condition : The HPLC system was a reverse-phase C18-coated silica gel column, 250 mm x 5 mm id, with a mobile phase of 3 volumes methanol and 1 volume water (final pH 6.7) at a flow rate of 1 mL/min. 100 μL samples of an approximate 1 mg/mL solution in the mobile phase were injected, and the emergence of the material was observed using refraction index detection.

Thirty-one reference compounds were used to generate the linear relationship between log k (k = capacity factor) and log Pow. Using the HPLC retention time for the peak of the test substance, the log k was determined, and the log Pow value was calculated using the linear equation developed from the reference compounds.

Log Pow was determined according to the following calculations:
Retention time (RT), min = 5.7
Capacity factor, k = 0.87, $k = (RT_{cmpd} - RT_{unretained\ std})/RT_{unretained\ std}$
log k = -0.06
linear equation: log k = -0.930 + 0.357 log Pow

Reliability : (1) Valid without restrictions
Reference Number (4.2)

2.6 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 8800 mg/l at 20 °C
GLP : no data
Test substance : Diisopropyl ether (CAS # 108-20-3)
Test substance : CAS No. 108-20-3; diisopropylether; purity is unknown.
Reliability : (2) valid with restrictions
The Ullmann's Encyclopedia of Industrial Chemistry is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag : Critical study for SIDS endpoint
Reference Number (8)

3.1 PHOTODEGRADATION

Type	:	Air
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1.5E6 OH- radicals/cm3
Rate constant	:	= .00000000002434 cm^3/(molecule*sec)
Degradation	:	= 50 % after 5.3 hour(s)
Method	:	other (calculated): Calculated values using AOPWIN version 1.89, a subroutine of the computer program EPIWIN version 3.12
Test substance	:	Diisoproply Ether (CAS # 108-20-3)
Method	:	Calculated values using AOPWIN version 1.89, a subroutine of the computer program EPIWIN version 3.12 Indirect photodegradation, or atmospheric oxidation potential, is based on the structure-activity relationship methods developed by R. Atkinson under the following conditions: Temperature: 25°C Sensitizer: OH- radical Concentration of Sensitizer: 1.5E6 OH- radicals/cm3
Remark	:	DIPE has the potential to volatilize to air, based on a vapor pressure of 19,865 Pa at 25°C (Daubert and Danner, 1989), where it is subject to atmospheric oxidation. In air, DIPE can react with photosensitized oxygen in the form of hydroxyl radicals (OH-). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPIWIN, 2000) calculates a chemical half-life for a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated), based on an OH- reaction rate constant and a defined OH- concentration. DIPE has a calculated half-life in air of 5.3 hours or 0.4 days (12-hour day), based on a rate constant of 24.34 E-12 cm3/molecule*sec and an OH- concentration of 1.5 E5 OH-/cm3.
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint
Reference Number		(6)

Test substance	:	Diisoproply Ether (CAS # 108-20-3)
Method	:	Technical discussion
Remark	:	Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer (Harris, 1982a). An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). The oxygen non-bonding electrons in ethers do not give rise to absorption above 160 nm, which is why pure ether solvents can be used in spectroscopic studies. Consequently, DIPE is not subject to photolytic processes in the aqueous environment.

Reliability	:	(2) valid with restrictions This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag	:	Critical study for SIDS endpoint
Reference Number		(27)

3.2 STABILITY IN WATER

Type	:	abiotic
GLP	:	no data
Test substance	:	Diisoproply Ether (CAS # 108-20-3)
Method	:	Technical discussion
Result	:	Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with leaving groups that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Gould, 1959). The lack of a suitable leaving group renders a compound resistant to hydrolysis. DIPE is resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive and Harris (1982b) identifies ether groups as generally resistant to hydrolysis. Therefore, hydrolysis will not contribute to the removal of diisoproply ether from the environment.
Reliability	:	(2) valid with restrictions This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag	:	Critical study for SIDS endpoint
Reference Number		(9) (11)

3.3 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level I
Media	:	other: air - biota - sediment(s) - soil - water
Method	:	Calculation according Mackay, Level I
Remark	:	Physicochemical data used in the calculation: Parameter Value w/ Units Molecular Weight = 102.18 Temperature = 25° C Log Kow = 1.52 Water Solubility = 8,800 g/m3 Vapor Pressure = 19,865 Pa Melting Point = -86.8° C
Result	:	Using the Mackay Level I calculation, the following distribution is predicted for diisoproply ether: %Distribution Compartment 97.83 Air 2.10 Water 0.06 Soil <0.01 Sediment <0.01 Suspended Sediment <0.01 Biota
Test substance	:	Diisoproply Ether (CAS # 108-20-3)
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated.

Flag : Critical study for SIDS endpoint
Reference Number (17)

Type : fugacity model level III
Media : air - sediment(s) - soil - water
Method : Level III simulation using the Mackay Multimedia Environmental Model (Mackay, 2001)

Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : Level III simulation using the Mackay Multimedia Environmental Model (Mackay, 2001). Mass balances are calculated for the four bulk media of air (gas + aerosol), water (solution + suspended sediment + biota), soil, (solids + air + water), and sediment (solids + pore water). Equilibrium exists within, but not between media. Physical-chemical properties are used to quantify a chemical's behavior in an evaluative environment. Three types of chemicals are treated in this model: chemicals that partition into all media (Type 1), non volatile chemicals (Type 2), and chemicals with zero, or near-zero, solubility (Type 3). The model can not treat ionizing or speciating substances. The Level III model assumes a simple, evaluative environment with user-defined volumes and densities for the following homogeneous environmental media (or compartments): air, water, soil, sediment, suspended sediment, fish and aerosols.

This model provides a description of a chemical's fate including the important degradation and advection losses and the intermedia transport processes. The distribution of the chemical between media depends on how the chemical enters the system, e.g. to air, to water, or to both. This mode of entry also affects persistence or residence time.

The rates of intermedia transport are controlled by a series of 12 transport velocities. Reaction half-lives are requested for all 7 media. The advective residence time selected for air also applies to aerosols and the residence time for water applies to suspended sediment and fish. The advective residence time of aerosols, suspended sediment and fish cannot be specified independently of the air and water residence times.

Result : Output

	Mass%	Half life(hr)	Emissions(kg/hr)
Air	19.4	25.2	1000
Water	61.0	360	1000
Soil	19.5	720	1000
Sediment	0.1	3240	0

Test condition : Physchem Inputs
Molar Mass = 102.18
Data Temperature = 25 ºC
Water Solubility = 8800 mg/l exp.
Vapour Pressure = 19865 Pa exp.
Log Kow = 1.52 exp.
Melting Point = -86.8 ºC exp.

Reaction Half Lives in hours (if not available they can be predicted using EPIWIN)

Air (gaseous)	25.2
Water (no susp. part.)	360
Bulk Soil	720
Bulk Sediment	3240
Suspended Particles	360
Fish	360
Aerosol	25.2

Environmental Properties (EQC standard environment)
Dimensions (all defaults)
Densities (all defaults)

Organic carbon & Advection (all defaults)
Transport Velocities (all defaults)

Emission and Inflows (defaults used)
Air 1000 kg/hr
Water 1000 kg/hr
Soil 1000 kg/hr
Sediment 0 kg/hr

Conclusion : The majority of DIPE is calculated to partition into the water phase, with smaller but significant amounts into air and soil, based on the modeling parameters used in this calculation. DIPE is considered to be a Type 1 chemical with potential to partition into all environmental compartments.

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated.

Flag : Critical study for SIDS endpoint

Reference Number (16) (18) (19) (20)

3.4 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Contact time : 28 day(s)
Degradation : 0% after 28 days
Result : not readily biodegradable
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1982
GLP : no
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Result : Test substance was not readily biodegradable. After 28 days, the test substance exhibited no measurable biodegradation. By day 5, >60% biodegradation of positive control was observed, which meets the guideline requirement. No excursions from the testing guideline were noted. The inhibition study showed that the test substance did not inhibit the biodegradability of the positive control substance, sodium benzoate.

Sample	% Degradation* (day 28)	Mean % Degradation (day 28)
Test Substance	0.0, 0.0	0.0
Na Benzoate	65.0, 73.0	69.0

* duplicate data

Mean oxygen concentrations (mg/L) of duplicate test systems:

Day 0
Mineral Salts Control = 8.85
Blank = 8.8
Na Benzoate = 8.95
Test Substance = 8.9 (single test system)
Test Substance + Na Benzoate = 8.9* (single test system)

Day 5
Mineral Salts Control = 9.0
Blank = 8.8
Na Benzoate = 5.7
Test Substance = 8..85
Test Substance + Na Benzoate = 5.8

Day 15
Mineral Salts Control = 8.75
Blank = 8.65
Na Benzoate = 4.9
Test Substance = 8.55
Test Substance + Na Benzoate = 4.9

Day 28
Mineral Salts Control = 8.65
Blank = 7.05
Na Benzoate = 3.6
Test Substance = 8.3
Test Substance + Na Benzoate = 4.15

Test condition : The inoculum source was the Sittingbourne Sewage works in Kent, England, and was prepared according to methods described in the OECD 301D guideline. The test substance was added to the test medium by direct addition at a concentration of 3.0 mg/L. Test systems were incubated at 20 ± 1 °C and biodegradation was determined by measuring the oxygen concentration on days 5, 15, and 28. Each sampling of the test substance and control was conducted in duplicate. The theoretical oxygen demand was 2.82 mg O2 per mg test substance and a theoretical carbon dioxide (CO2) evolution of 2.59 mg CO2 per mg test substance. Sodium benzoate was used as the positive control.

The purity of the test substance was not supplied, but the infra-red spectrum of the test substance matched a published standard (density = 0.723 to 0.726 kg/L). The test substance was stored in the dark at ambient temperature. Nitrogen was blown over the surface of the material when the container was opened and exposed to air in order to minimize peroxide formation.

Conclusion : Diisopropyl ether is not readily biodegradable and it did not significantly inhibit the biodegradability of the test substance in an inhibition test.

Reliability : (1) valid without restriction

Reference Number (22)

Type :
Inoculum : other: sanitary waste treatment plant effluent
Contact time : 5 day(s)
Degradation : (±) % after
Result :
Deg. product :
Method : other: American Public Health Association; No. 219 5-Day BOD; Standard Dilution Method
Year : 1971
GLP : no
Test substance : other TS: diisopropyl ether (CAS No. 108-20-3)
Remark : Test type: Biological Oxygen Demand (BOD)
Result : 0.19 g O2/g test material at 20 ± 1°C
The theoretical oxygen demand (ThOD) of the test substance was 2.82.
The percent ThOD in 5 days was 7%.

The article stated that the only deviation from the standard method was the addition of 0.5 mg/L allylthiourea to prevent nitrification.

Test condition : The article stated that the test method followed APHA Standard Method No. 219 (1971). The test was run at a temperature of 20 ± 1°C. 500-mL test solutions were seeded with a filtered 10-mL volume of the effluent from a biological sanitary waste treatment plant. The activity of the inoculum was check by including a treatment containing a mixture of glucose and glutamic acid. Test mixtures were stirred using a magnetic stirrer.

Conclusion : 5-day BOD = 0.19 g/g, representing 7% biodegradation of the test substance.

Reliability : (2) valid with restrictions

The article presented a brief description of the testing methods, but cited a reliable guideline method in use at the time of the study.

07.02.2006 (1.1)

Type	:	aerobic
Inoculum	:	activated sludge
Deg. product	:	
Method	:	other: (comparison study of three aerobic biodegradation methods)
Year	:	1997
GLP	:	no
Test substance	:	other TS: diisopropyl ether (CAS No. 108-20-3)
Method	:	Comparison study of three aerobic biodegradation methods) Continuous Biological Treatment: (1) EPA Method 304B (EPA, 1994) Batch Methods: (2) Batch Oxygen addition (BOX) (Rajagopalan et al., 1998), and (3) Serum Bottle Test (SBT) (Rajagopalan et al., 1998)
Remark	:	Exposure Period: Method 304: 30 days BOX: 0.5 to 2 hours SBT: 0.5 to 2 hours
Result	:	The average percent removal of the test substance in the continuous activated sludge unit (EPA Method 304B) was 99.4%. Three experimental trial runs with each of the three biodegradation methods yielded the following average first-order biodegradation rate constants (K1 = L/g Volatile Suspended Solids-h) for the test substance: K1 (L/g VSS-h) 304B 98 BOX 17.4 SBT 19.2
Test condition	:	A pilot-scale continuous activated sludge unit served as the source of biomass for kinetic rate constant comparisons of the three methods. The activated sludge was acclimated in the pilot unit by feeding a synthetic cocktail of eight volatile organic compounds during a 2-month equilibration period. Equilibration and testing was done at ambient temperature (22 to 24°C). The hydraulic retention time (HRT) was 7.7 hours and the solids retention time (SRT) was 33 days. Average organic removal efficiencies based on COD and TOC were 92 and 88%, respectively. During the biodegradation testing using Method 304B, feed and effluent samples were collected in headspace-free VOA vials and stored at 4°C until analyzed. Samples were analyzed by purge-and-trap gas chromatography using a flame ionization detector. Triplicate biodegradation runs on the test compound were conducted with at least six influent and effluent samples taken at 1 HRT (approx. 8 hours) intervals. The two batch biodegradation testing methods (BOX and SBT) used activated sludge biomass from the pilot-scale reactor. Biomass was diluted using effluent from the system to achieve range of 200 to 600 mg/L. The test compound was injected into the batch reactors and the concentration was monitored over time by collecting gas samples directly from the headspace using an automatic sampling pump and analyzing immediately using gas chromatography.
Conclusion	:	The authors indicated that K1 values >10 L/g VSS-h represent readily biodegradable organic compounds. Based on the results of this study, all three test methodologies showed the test substance to be effectively utilized by activated sludge microorganisms under aerobic conditions.
Reliability	:	(2) valid with restrictions The publication presented a well-documented study based on ound scientific principles.

07.02.2006 (2.1) (20.3) (24.2)

Type	:	aerobic
Inoculum	:	other: Mixture (see remarks)
Contact time	:	600 day(s)
Degradation	:	(±) % after
Result	:	
Deg. product	:	
Method	:	other: (continuous-flow bioreactors)
Year	:	2001
GLP	:	no
Test substance	:	other TS: diisopropyl ether (CAS No. 108-20-3)
Remark	:	Inoculum consisted of a mixture of the following: 1) mixed liquor from the Metropolitan Sewer District (MSD), Cincinnati, OH, 2) mixed liquor from Shell Development Co., Houston, TX, and 3) aquifer material wash water from a MTBE-contaminated site in Port Hueneme, CA.
Result	:	The authors indicated that removal of DIPE was comparable to that achieved for MTBE, which was greater than 99.9%.
Test condition	:	Bioreactors (Autoclave Engineers, Erie, PA) were initially seeded with 2 L of mixed liquor from the MSD, 600 mL of mixed liquor from Shell Development Co., and 140 mL of aquifer wash water. Cultures were maintained on a total influent feed of 417 mg/L chemical oxygen demand (COD) divided as 50% methyl tert-butyl ether (MTBE) and 50% as diisopropyl ether (DIPE). Reactors were well mixed and controlled to a temperature of 20°C. To retain high biomass levels, a polyethylene porous pot was inserted into the reactor. The pots consisted of 0.45 cm thick filter-grade polyethylene (pore size = 20 mm), with an internal diameter of 19.1 cm and a height of 29.2 cm. Initially, a solids retention time of 18 days was maintained by wasting intentionally from the reactor. Subsequently (after about 120 days) intentional wasting ceased and only took place during sampling of the reactors. The combined influent flow rate was 2.37 L/d, with 80% of the total flow provided by a pH-adjustment solution, and 20% provided by an acidified nutrient solution. The pH-adjustment solutions contained deionized water, MTBE and DIPE fed by a syringe infusion pump, and an appropriate amount of 10N sodium hydroxide to maintain the pH between 7.4 and 8.0. The nutrient solution consisted of deionized water with essential salts and vitamins added to promote biological growth. Final nutrient concentrations inside the reactor were as follows: (NH4)2SO4, 93 mg/L; MgSO4, 69.6 mg/L; CaCl2o2H2O, 22.5 mg/L; K2HPO4, 6.9 mg/L; CuSO4oH2O, 0.08 mg/L; Na2MoO4o2H2O, 0.15 mg/L; MnSO4oH2O, 0.13 mg/L; ZnCl2, 0.23 mg/L; CoCl2o6H2O, 0.42 mg/L; and FeCl2o4H2O, 17.25 mg/L.. The hydraulic retention time was 4.2 days with a total reactor volume of 9.95 L and an enrichment culture volume of 6 L. Effluent from the reactors was monitored weekly for the presence of MTBE and DIPE using gas chromatography equipped with a flame ionization detector (FID) and a 60/80 Carbopack B5% Carbowax 20 M glass column. The pH of the system was measured daily, and COD and dissolved organic carbon (DOC) was measured weekly.
Conclusion	:	Diisopropyl ether can be effectively biodegraded in high biomass aerobic reactors.
Reliability	:	(2) valid with restrictions The report provided adequate details of the test conditions but reported only a text description of biodegradation results.

07.02.2006 (20.2)

Type	:	

Inoculum	:	other: soil and groundwater from a site previously exposed to methyl tert-butyl ether
Contact time	:	1 year
Degradation	:	(±) % after
Result	:	
Deg. product	:	
Method	:	other: (soil/water microcosm)
Year	:	1999
GLP	:	no
Test substance	:	other TS: diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: soil/water microcosm
Result	:	No detectable biodegradation of the test substance occurred after one year of incubation.
Test condition	:	Soil and water from an aquifer with previous exposure to methyl tert-butyl ether (MTBE) was collected using a coring device and a pump. The material was brought to the laboratory where the sediment was thoroughly mixed. Groundwater was filtered through a 0.45 mm filter and sparged for 12 hours with sterile air to oxygenate the water and to remove background volatile chemicals. Analysis by gas chromatography indicated that concentrations of MTBE in the aqueous samples were <10 mg/L. Microcosms were constructed in amber 255-mL screw-top bottles sealed with TeflonÒ MininertÒ valves. Each bottle contained 150 g of wet sediment, 140 mL of sterile groundwater and 3000 mg/L of diisopropyl ether (DIPE). Treatments were constructed in triplicate with matching abiotic controls. Sediment used for the abiotic controls was autoclaved for one hour on each of three consecutive days. Additionally, 250 mg/L of mercuric chloride was added to ensure no biological activity. Microcosms were incubated in the dark at 16 °C. All samples were analyzed every 30 days by purge and trap gas chromatography and flame ionization detection to determine concentrations of the test substance. Test substance disappearance relative to abiotic controls was the principal indicator of biodegradation.
Conclusion	:	The test substance was not aerobically biodegraded by indigenous subsurface microflora.
Reliability	:	(2) valid with restrictions The testing method did not follow any specific regulatory guideline method, but the publication provided valuable information using sound scientific principles.

07.02.2006 (26.1)

Type	:	anaerobic
Inoculum	:	other: sediment and groundwater from an anoxic aquifer polluted by municipal landfill leachate
Contact time	:	252 day(s)
Degradation	:	(±) % after
Result	:	
Deg. product	:	
Method	:	other: (closed serum bottle test)
Year	:	1993
GLP	:	no
Test substance	:	other TS: diisopropyl ether (CAS No. 108-20-3)
Result	:	Biodegradation Rate (ppm C/day) = 0 Methane recovery (% theoretical) = 0
Test condition	:	Diisopropyl ether was tested for the ability of the compound to be completely biodegraded to methane in an aquifer slurry. Sediment and groundwater were collected from a methanogenic portion of a shallow anoxic aquifer polluted by municipal landfill leachate. Slurries were prepared by placing 50 g of sediment and 75 mL of groundwater in sterile 160-mL serum bottles. The bottles were sealed with Teflon-lined stoppers and incubated in the dark at room temperature. Diisopropyl ether was added to the incubation mixture to reach an initial substrate concentration

of 50 ppm C. Pressure increases resulting from biogas formation (CH4 and CO2) were monitored with an automated pressure transducer system. The acclimation time was estimated as the amount of time where no significant pressure difference was measured between the substrate-amended treatment and un-amended controls.

At the end of the incubation period, biodegradation was measured as the depletion of parent substrate and the formation of methane over background controls. Measurements were made using gas chromatography equipped with a flame ionization detector. A 1.8 m x 0.32 cm 80/100 porapak Q column or a 0.2% Carbowax 1500 on Carbopack C column were used for headspace methane analyses and test substance determinations, respectively. Autoclaved controls were similarly assayed and were uniformly unable to exhibit methane formation or test substance disappearance. The amount of methane formed in aquifer incubations was compared to that theoretically expected based on the Buswell equation.

Conclusion : Diisopropyl ether was a persistent molecule that resisted anaerobic destruction. After 252 days, no evidence for the anaerobic biodegradability of diisopropyl ether was obtained.

Reliability : (2) valid with restrictions
The publication reported a well-documented study that meets basic scientific principles.

07.02.2006 (24.1)

Type : anaerobic
Inoculum : other: Sediment and surface or groundwater
Deg. product :
Method : other: unknown
Year : 1994
GLP : no
Test substance : other TS: diisopropyl ether (CAS No. 108-20-3)
Remark : Exposure period: 85, 180, or 244 days
Result : Biodegradation of diisopropyl ether with sulfate or nitrate available as electron acceptors:

	SO4 or NO3 Substrate Loss (%)	Amount Consumed (% Theoretical)	Rate (umol/SO4/day)
sulfate-reducing	0	0	0
nitrate-reducing	0	0	0

Biodegradation of diisopropyl ether under methanogenic conditions:

	Degradation Rate (ppm C/day)	Methane Recovery (% Expected)
Fuel-impacted river sediment	0	0
Industrial/sewage impacted creek sediment	0	6

Test condition : Several tests were carried out to determine the anaerobic biodegradation of the test substance. Three experiments were done to determine biodegradation under sulfate- and nitrate-reducing conditions and under methanogenic conditions. Sediment and surface water (or groundwater) from three sources were used as inoculum in separate experiments; (1) sediment/groundwater from a landfill leachate impacted aquifer, (2) sediment/surface water from a river historically impacted by oil storage and barge loading facilities, and (3) sediment/surface water from a creek impacted by industrial waste and domestic sewage sludge.

Slurries were prepared by placing 50 g of sediment and 75 mL of water into sterile 160-mL serum bottles. Water was amended with sodium sulfide (1 mM) and resazurin (0.0002%) to serve as reductant and redox indicator, respectively. The bottles were sealed with stoppers and the headspace

above the slurries was adjusted to 80% N2:20%CO2 (1 atm). To the landfill leachate-impacted samples, either sodium sulfate (5mM) or sodium nitrate (8 mM) was added in order to assess potential test substance decay coupled with the consumption of these electrons (referred to as sulfate-reducing and nitrate-reducing incubations, respectively). The test substance was added to the slurries to give an initial concentration of 50 ppm C. The rates of methane production, sulfate reduction, and nitrate depletion were monitored in slurries receiving the test substance and compared to test substance-free controls. All incubations were done in the dark at 24°C. The sulfate-reducing experiment was run for 244 days, the nitrate-reducing experiment was run for 85 days, and the methanogenic experiment was run for 180 days.

In the methanogenic incubations, increases in headspace pressure were routinely monitored. Parent compound depletion and formation of methane were confirmed by gas chromatography (GC). The net amount of sulfate and nitrate depletion over the controls was monitored by high pressure liquid chromatrography (HPLC).

Conclusion : Diisopropyl ether is not anaerobically degraded under nitrate- or sulfate-reducing conditions, and it is not anaerobically degraded under methanogenic conditions.

Reliability : (2) valid with restrictions
The publication reported a well-documented study that meets basic scientific principles.

07.02.2006 (20.1)

Type : aerobic
Inoculum : other: Gordonia terrae strain IFP 2001 (CNCM Registration No. CTP 1-1889); isolated from activated sludge taken at an urban waste water treatment plant
Contact time : 24 hour(s)
Degradation : (±) % after
Result :
Deg. product :
Method : other: (sealed flasks, shaken)
Year : 2000
GLP : no
Test substance : other TS: diisopropyl ether (CAS No. 108-20-3)
Result : Diisopropyl ether was degraded by 78% over the 24-hour incubation period.

Comparison of DIPE biodegradation to ETBE:

Test Substance	Degradation (%)
ETBE	100

The authors indicated concentrations of the test substance in the flasks were quantified by analytical means. The method was not described in the report, but was referenced in an earlier publication by the same workers.

Test condition : The capacity of ethyl t-butyl ether (ETBE)-induced resting cells of the inoculum to degrade diisopropyl ether was tested in sealed flasks. The article focused on biodegradation of ETBE, methyl t-butyl ether (MTBE) and t-amyl methyl ether (TAME), but was tested on other ethers including diisopropyl ether (DIPE).

G. terrae IFP 2001 was cultivated on ETBE-supplemented MM medium. After 24 hours incubation, bacteria were harvested by centrifugation (20,000 g for 20 minutes), washed twice in 100 mM Tris-HCl buffer at pH 7.0 and re-suspended in Tris-HCl. The test substance was added to 20-mL cell suspensions in 125-mL sealed flasks. Flasks were incubated for 24 hours at 30 °C with orbital shaking. Initial cell concentration was 0.5 g/L. The test substance was tested at 100 mg/L. Filtered samples were analyzed at 0-hour and 24-hours.

Conclusion : Diisopropyl ether was degraded by 78% within 24 hours.
Reliability : (2) valid with restrictions
Information on the analytical method was not provided in the report.
07.02.2006 (11.1)

3.5 BIOACCUMULATION

Species : other: see remark
Exposure period : at 25 °C
BCF : = 2.95
Method : other: calculation
GLP : no
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Remark : A log bioconcentration factor (BCF) of 0.47 is calculated (BCF = 2.95). With respect to a log Kow = 1.52, which was used to calculate the BCF, diisopropyl ether in the aquatic environment is expected to have a low bioaccumulation potential.
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Reference Number (6)

Species : other: see remark
Exposure period : at 25 °C
BCF : = 14.06
Method : other: calculation
GLP : no
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Remark : A log bioconcentration factor (BCF) of 1.15 is calculated (BCF = 14.06). With respect to a log Kow = 2.4, which was used to calculate the BCF, diisopropyl ether in the aquatic environment is expected to have a low bioaccumulation potential.
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Reference Number (6)

3.6 ADDITIONAL REMARKS

Memo : Biodegradation of diisopropyl ether

Remark : The article reports on a U.S EPA and American Petroleum Institute workshop (February 1-3, 2000) on biodegradation of methyl tert-butyl ether (MTBE)-contaminated soils and groundwater. MTBE is one of a group of structurally similar compounds commonly called alkyl ether oxygenates (AEO) that are added to reformulated gasoline to reduce carbon monoxide and ozone emissions. Diisopropyl ether (DIPE) is one type of AEO that is used in gasoline along others in this class of chemicals. The workshop focused on the status of the current research and understanding on biodegradation of MTBE and reported relevant information on the biodegradation of DIPE and other AEOs used in reformulated gasoline.

Pure microbial cultures have been identified and isolated that have demonstrated the capability of utilizing MTBE as a sole carbon and energy source under aerobic conditions (Scow et al., 2000). This isolate, bacterial strain PM1, was studied by Church and Tratnyek (2000) to determine the aerobic degradation pathway of MTBE. In their study, the authors confirmed the mineralization of MTBE and determined the degradation rates of DIPE and other AEOs were of the same order of magnitude as the

degradation rates of MTBE (Church and Tratnyek, 2000). Their results suggested that similar enzyme systems were responsible for all of the reactions.

While the majority of research on anaerobic biodegradation of these compounds has been unable to show that MTBE is utilized, a few studies have demonstrated that MTBE and other AEOs may be susceptible to attack under anaerobic conditions. Kropp et al. (2000) studied the anaerobic biodegradation potential of MTBE, DIPE, and other oxygenates in sediment slurries under methanogenic conditions. They found definite evidence in the form of methane and carbon dioxide production to conclude that anaerobic degradation was occurring. The workshop authors concluded that anaerobic biodegradation was a phenomena that was not widespread and extremely difficult for these compounds.

07.02.2006 (2.2) (4.3) (13.1) (21.1)

Memo : Biodegradation of diisopropyl ether under aerobic and anaerobic conditions - summary

Remark : Diisopropyl ether (DIPE) is one of a group of similar compounds referred to as alkyl ether oxygenates (AEO) that are added to reformulated gasoline. Biodegradation studies with DIPE and other AEO compounds have demonstrated the ability of these substances to be consumed by pure strains and mixed cultures of bacteria when incubated under aerobic conditions. Church and Tratnyek (2000) showed that bacterial strain PM1, which had been acclimated to methyl t-butyl ether (MTBE), could mineralize MTBE and demonstrated similar degradation rates for DIPE and other AEOs. They concluded that similar enzymes were responsible for all the degradation reactions. Additional evidence showing the wide spectrum of activity of the bacterial enzyme systems to degrade AEOs was provided by Hernandez-Perez et al. (2001). Using isolated Gordonia terrae (strain IFP 2001) that had been grown on ethyl t-butyl ether (ETBE), degradation of a variety of other AEOs could be achieved. DIPE was degraded 78% within 24 hours in their study (Hernandez-Perez et al. 2001).

Optimum biodegradation in mixed culture systems occurred when the microbial culture is allowed a period of acclimation to the substrate. For example, Bridié et al. (1979) measured only 7% consumption of the theoretical oxygen demand when DIPE was tested in a 5-day BOD test. In contrast, Cano et al. (1999) showed rapid utilization of DIPE when activated sludge was conditioned to a cocktail of volatile organic compounds for two months. In a continuous flow reactor, DIPE removal averaged 99.4%. Cano et al. (1999) also measured high rates of biodegradation of DIPE when comparing the continuous treatment method (EPA Method 304B) (EPA 1994) to two batch treatment methods (BOX and SBT methods; Rajagopalan et al. 1998). Based on the measured rate constants, the authors considered DIPE to be readily biodegradable. Pruden et al. (2001) also observed high removal rates (e.g., 99.9%) of DIPE through a continuous flow reactor system. The performance of the reactors was enhanced when biomass was retained in the reactor, suggesting that a long biomass residence time may be needed for complete mineralization.

Biodegradation of DIPE is not always observed in biodegradation assays. Zenker et al. (1999) failed to show biodegradation of DIPE over a 1-year period using indigenous microflora in sediment and water from an aquifer that had been previously exposed to MTBE. Given the apparent need of microbial communities for a period of acclimation to DIPE, it is unlikely that DIPE would be considered readily biodegradable in standard guideline studies. However, the evidence shows that DIPE can be inherently degraded by pure strains of bacteria and mixed enrichments of activated sludge microorganisms.

While available research shows that DIPE is capable of being biodegraded under aerobic conditions, anaerobic biodegradation is extremely difficult and this substance is considered recalcitrant under those conditions. Suflita et al. (1993) showed no biodegradation of DIPE after 252 days of anaerobic incubation. Substrate was added as 50 ppm C to sediment and groundwater collected from a methanogenic portion of a shallow anoxic aquifer. Similarly, DIPE was evaluated for anaerobic biodegradability under methanogenic conditions as well as sulfate and nitrate-reducing conditions (Mormile et al. 1994). Inocula from three sources (e.g., sediment/groundwater from an aquifer impacted by landfill leachate, sediment/surface water from a river impacted by oil storage, and sediment/surface water from a creek impacted by industrial waste and domestic sewage) were used in separate incubations to assess anaerobic biodegradation in sealed serum bottles. No DIPE biodegradation was measured over incubation periods of 85 days (nitrate-reducing conditions), 180 days (methanogenic conditions), and 244 days (sulfate-reducing conditions). Lack of methane production reported by Suflita and Mormile (1993) does not preclude partial anaerobic biodegradation of DIPE in their studies because only methane was monitored. Kropp et al. (2000) studied the anaerobic biodegradation potential of a number of AEOs including DIPE in sediment slurries under methanogenic conditions. They found evidence in the form of methane and carbon dioxide production to conclude that anaerobic biodegradation was occurring, although the authors stated that anaerobic biodegradation was not a widespread phenomena and extremely difficult for these compounds.

07.02.2006

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	*Pimephales promelas* (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 91.7
Analytical monitoring	:	yes
Method	:	other: Flow-through Fish Acute Toxicity Test
Year	:	1983
GLP	:	no data
Test substance	:	Diisopropyl Ether (CAS No. 108-20-3)
Method	:	The water solubility of the test chemical was obtained from literature or determined experimentally. A flow through system using proportional diluters and modified continuous mini-diluter system was used for maintaining the required test concentrations Twenty to twenty-five 30 day-old fish, each weighing approximately 0.12 g, were randomly divided amongst the test tanks (control and five different concentrations) with flow-through dilutor systems. Lake Superior water maintained at 25°C ± 1°C was used in the test. Routine measures of hardness (EDTA) and total alkalinity of test water yielded mean values of 45.5 and 42.2 mg/L as CaCO3, respectively. The arithmetic mean of the pH was 7.5 and dissolved oxygen was always greater than 60% of saturation. Fish were supplied from the United States Environmental Protection Agency, Environmental Research Laboratory-Duluth culture. They were not fed during the test. Deaths were recorded after 1, 3, 6,12, 24, 48, 72, and 96 hours.
Remark	:	Statistics: Trimmed Spearman-Karber Method Test method described in reference.
Result	:	96-hour LC50 = 91.7 mg/L based upon measured values Analytical method used was GC analysis with Flame Ionization Detection (GC-FID), performed on a Hewlett-Packard model 5730A gas chromatograph. Concentrations of the test chemical were measured daily at each exposure level.
Conclusion	:	96-hour LC50 = 91.7 mg/L based upon measured values.
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because complete information on the analytical results were not available and the study was not conducted under GLP.
Flag	:	Critical study for SIDS endpoint
Reference Number		(25)

Type	:	Calculation
Species	:	Fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 214.1
Method	:	other: ECOSAR version 0.99h, US EPA
Test substance	:	Diisopropyl Ether (CAS No. 108-20-3)
Method	:	ECOSAR version 0.99h, US EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition

coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound.

To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.

Result : LC50, 96 h, for fish = 214.1 mg/L

Test condition : Experimental water solubility, 8800 mg/l @ 20°C (Heitmann, W et al, 1987), log Kow, 1.52 (Funasaki, N et al, 1985) and melting point, -86.6°C (SRC PhysProp database) were entered into the program.
Class: Neutral organics

Conclusion : The predicted 96 h LC50 value for fish (214.1 mg/L) is in good agreement with the experimental 96 h LC50 value for fathead minnow (Pimephales promelas) (91.7 mg/L) (Veith et al., Can. J. Fish. Aquat. Sci., 40:743-748) and 48 h EC50 value for Daphnia (190.0 mg/L) (Stephenson R.R., Shell Research Limited, Report No. SBGR.83.215).

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.

Reference Number (5)

Type : flow through
Species : *Pimephales promelas* (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/L
LC50 : = 786 mg/L
EC50 : = 476 mg/L
Analytical monitoring : yes
Method : other: Flow-through Fish Acute Toxicity Test
Year : 1983
GLP : no data
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : Test solutions were prepared using a proportional diluter system without replication. This system provided control and five test substance concentrations to glass test vessels. Each vessel held 2 L of test solution and the diluter flow rate was sufficient to provide 18 volume additions per day. An aqueous stock solution of 1050 mg/L was used by the diluter to prepare the exposure series. Dilution water was filtered Lake Superior water. Typical ranges of water quality factors measured in this water were pH (7.4 – 8.2), total hardness (44 – 53 mg/L as $CaCO_3$), and specific conductance (78 – 86 μmhos/cm).

Test fish originated from in-house cultures of *P. promelas* at the U.S. EPA Environmental Research Laboratory – Duluth. Fish were not fed 24 h prior to testing or during the test. At test initiation, fish were randomly placed in

test vessels until each vessel contained 10 individuals. Individuals used in testing were 34 d old and measured 19.0 mm mean length (SD = 2.534) and 0.104 g mean weight (SD = 0.0433). Biomass loading was 1.04 g/L. Death was the major test endpoint. Numbers of dead fish were counted daily and any dead fish were removed from the vessels. Abnormal behavioral changes were recorded at each observation time. LC50 (lethality) and EC50 (total effect) values were determined.

Temperature, dissolved oxygen, and pH were measured daily in all test chambers. Mean values (and Standard Deviation) were 24.9 °C (SD = 0.52), 7.3 mg/L (SD = 0.13), and 7.75 (SD = 0.16), respectively. Total hardness and alkalinity were measured once in the control, low, medium, and high test levels. Mean values were 43.7 mg/L total hardness as $CaCO_3$ (SD = 0.96) and 49.6 mg/L alkalinity as $CaCO_3$ (SD = 0.25). Lighting was provided by fluorescent bulbs that produced 28 to 48 lumens/sq ft at the water surface. The photoperiod was 16 h light and 8 h dark.

Test substance concentrations were verified in most cases daily during the test using gas-liquid chromatography. Concentrations were averaged and a mean percent recovery was calculated. The nominal with measured concentrations in parentheses were, control (not detected), 157 mg/L (131 mg/L), 242 mg/L (210 mg/L), 373 mg/L (382 mg/L), 574 mg/L (594 mg/L), and 883 mg/L (1044 mg/L). The overall percent recovery was 98.7%.

Remark : Statistics: LC/EC50 values determined by Trimmed Spearman-Karber Method

Result : 96-hour LC50 = 786 mg/L based on mean measured values.
96-hour EC50 = 476 mg/L based on mean measured values.

The EC50 value was based on mortality and the following abnormal effects: loss of schooling behavior, swimming near the surface, hypoactive, under-reactive to external stimuli, loss of equilibrium.

Conclusion : 96-hour LC50 = 786 mg/L based on mean measured values.
96-hour EC50 = 476 mg/L based on mean measured values.

Reliability : (1) valid without restrictions

Reference Number (7)

Type : flow through
Species : *Pimephales promelas* (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/L
LC50 : = 900 mg/L
Limit test
Analytical monitoring yes
Method : other: Flow-through Fish Acute Toxicity Test (ASTM, 1980)
Year : 1985
GLP : no data
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : Test solutions were prepared using a continuous-flow diluter delivery system, which delivered four test substance concentrations and control solutions to duplicate test vessels. Dilution water was filtered Lake Superior water. Average values for water quality factors for the dilution water were: hardness (44.6 mg/L as $CaCO_3$), total alkalinity (44.0 mg/L as $CaCO_3$), and pH (7.6). Test chambers were glass vessels and contained 2 L of test solution. Solution flow rates through the test chambers was sufficient to provided at least a 95% replacement in approximately 4 h. Test substance concentrations were verified daily during the test using either gas chromatography or high pressure liquid chromatography methods.

The mean temperature for the test was 25 ± 0.5°C, and dissolved oxygen remained at or above 80% saturation. Lighting was provided by wide spectrum fluorescent bulbs at an intensity of 22 to 38 lumens/sq ft over the test chambers. The photoperiod was 16 h light and 8 h dark with a 30-min

dusk/dawn transition period.

Test fish originated from cultures maintained by the U.S. EPA Environmental Research Laboratory – Duluth, MN. and were 28 to 34 days old (weighing approximately 0.12 g) at the time of testing. A total of 20 fish per treatment (10/replicate) was used in the test. Fish were added to the test chambers 2-3 h before introduction of the test solutions. Fish were not fed 24 h before or during the test. Mortalities were recorded daily.

Remark : Statistics: Trimmed Spearman-Karber Method or log-probit method.
Result : 96-h LC50 = 900 mg/L based on measured concentrations
95% CL = 881 – 920 mg/L
Conclusion : 96-h LC50 = 900 mg/L based on measured concentrations
Reliability : (1) Valid without restrictions.
Reference Number (1.2)

Type : static
Species : *Carassius auratus* (Fish, fresh water)
Exposure period : 24 hours
Unit : mg/L
LC50 : = 380 mg/L
Analytical monitoring yes
Method : other: static acute fish toxicity test (APHA, 1971)
Year : unknown
GLP : no data
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : The test consisted of exposing groups of six fish to a series of concentrations of the test substance for 24 h. Fish were exposed in an all glass tanks holding 25 liters of test solution. Dilution water was local tap water having the following characteristics (all values in mg/L):
Cl^{-} = 65; NO_2^{-} = 0; NO_3^{-} = 4; SO_4^{-2} = 35; PO_4^{-3} = 0.15; HCO_3^{-} = 25; SiO_2 = 25; NH_4^{+} = 0; Fe = 0.05; Mn = 0; Ca^{+2} = 100; Mg^{+2} = 8; alkali as Na^{+} = 30; pH = 7.8.

The test was run at a temperature of 20±1°C, and the solutions were not aerated during the test period.

Test fish had a mean length of 6.2±0.7 cm, a mean weight of 3.3 ± 1.0 g and were in good health at the time of testing.

Exposure concentrations were confirmed either by total organic carbon analysis or by extraction and subsequent analysis by gas chromatography. Measured concentrations were not reported in this study.

Remark : Determination of LC50 by graphical interpolation of log concentrations versus percent mortality (APHA, 1971).
Result : 24-hour LC50 = 380 mg/L

The analytical method was either total organic carbon analysis or gas chromatography. It was not reported what method was employed for this test substance nor if the result was based on measured concentrations.

Conclusion : 24-hour LC50 = 380 mg/L.
Reliability : (3) not reliable
The test was run for only 24 hours to ensure that the dissolved oxygen content did not fall below 4 mg/L. The report lacked sufficient detail for assessment. It was not stated whether results were based on nominal or measured values.
Reference Number (1)

Type : static
Species : *Lepomis macrochirus* (Fish, fresh water)
Exposure period : 96 hours
Unit : mg/L
LC50 : 7000 mg/L
Analytical monitoring : no
Method : other: static acute fish toxicity test

Year	:	not stated
GLP	:	no
Test substance	:	Diisopropyl Ether (CAS No. 108-20-3)
Method	:	The test consisted of exposing groups of fish to a four-dilution series of the test substance for a period of 96 h. Test vessels were all glass 5-gallon aquaria. The volume of test solution was adjusted to assure that a biomass loading was no more than 1 g fish /liter solution. Dilution water was well water having a typical pH of 7.6 to 7.9 and a hardness of 55 mg/L (as $CaCO_3$). Fish were obtained from a commercial source and assessed for health during a 14-d acclimation period prior to testing. During that time they were maintained on a commercial fish food diet supplemented with minced frozen shrimp. Fish were not fed 48 hours prior to testing. Fish were randomly selected for testing and were approximately 33 to 75 mm in length. The test was run at 23°C. Test solutions were not aerated for the initial 24 h, but aeration was applied thereafter if the dissolved oxygen concentration was being depleted. Dissolved oxygen readings were taken daily, and pH was measured at the end of the test. However, these data were not provided in the report. Mortality was assessed daily and any dead fish were removed at each observation time.
Remark	:	The LC50 was determined by plotting survival percentages on semi-logarithmic paper and drawing a straight line fit through or near significant points above and below 50% survival.
Result	:	96-hour LC50 = 7,000 mg/L The mortality pattern reported for the test substance suggests that a more likely estimate of the LC50 value would lie between 7,900 and 10,000 mg/L, rather than 7,000 mg/L. This was due to a non-monotonic dose response pattern of mortality. The report authors indicated that the LC50 value was higher than the published solubility for the test substance.
Conclusion	:	96-hour LC50 = 7,000 mg/L based on nominal concentrations
Reliability	:	(3) not reliable Documentation was insufficient for evaluation. Basic water quality data during the test were not provided. The authors stated that aeration of the test solutions was used after 24 hours to ensure maintenance of dissolved oxygen. No analytical verification of exposure concentrations were made. It is likely that test material was lost from the test medium during exposure.
Reference Number		(4.1)

Type	:	static
Species	:	*Menidia beryllina* (Fish, estuarine/marine)
Exposure period	:	96 hours
Unit	:	mg/L
LC50	:	6600 mg/L
Analytical monitoring	:	No
Method	:	other: static acute fish toxicity test
Year	:	not stated
GLP	:	no
Test substance	:	Diisopropyl Ether (CAS No. 108-20-3)
Method	:	The test consisted of exposing groups of fish to a four-dilution series of the test substance for a period of 96 h. Test vessels were all glass 5-gallon aquaria. The volume of test solution was adjusted to assure that a biomass loading was no more than 1 g fish /liter solution. Dilution water was prepared by adding “instant ocean” salts to well water (pH of 7.6 to 7.9; hardness 55 mg/L (as $CaCO_3$) until a specific gravity of 1.018 was achieved. Fish were field collected in nets from Horseshoe Bay at Sandy Hook, New Jersey. They were held for a 14-d acclimation period prior to testing and assessed for health during that time. During the acclimation period they

were fed minced frozen shrimp. Fish were not fed 48 hours prior to testing. Fish were randomly selected for testing and were approximately 40 to 100 mm in length.

The test was run at 20°C, and test solutions were continuously aerated during the exposure period. Dissolved oxygen readings were taken daily, and pH was measured at the end of the test. However, these data were not provided in the report.

Mortality was assessed daily and any dead fish were removed at each observation time.

Remark : LC50 determined by graphical interpolation of the logarithm of the concentration versus the percentage mortality

Result : 96-hour LC50 = 6600 mg/L

The mortality pattern reported for the test substance does not correspond with the estimated LC50 value. Given the dose-response pattern, the LC50 value would lie between 3,200 and 5,000 mg/L, rather than 6,600 mg/L. The authors reported that the result was higher than the reported water solubility of the test substance.

Conclusion : 96-hour LC50 = 6600 mg/L based on nominal concentrations

Reliability : (3) not reliable
Documentation was insufficient for evaluation. Basic water quality data during the test were not provided. The authors stated that aeration of the test solutions was used after 24 hours to ensure maintenance of dissolved oxygen. No analytical verification of exposure concentrations were made. It is likely that test material was lost from the test medium during exposure.

Reference Number (4.1)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Static
Species : *Daphnia magna* (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 190
Analytical monitoring : no
Method : other: U.S. Environmental Protection Agency, Methods for acute toxicity testing with fish, macro-invertebrates and amphibians (EPA-660/3-75-009)
Year : 1975
GLP : No
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Remark : Statistics:
Probit analysis after log transformation of the concentrations (Finney, 1971)
Probit Analysis, Finney, D.J., Cambridge University Press, 3rd edition, p333 (1971)

Result : The 24 h and 48 h Effect Concentration (EC50) values were calculated to be 240 mg/L (95% fiducial limits 210 to 280 mg/L) and 190 mg/L (95% fiducial limits 160 to 220 mg/L), respectively.
The immobilization (%) of Daphnia magna (n=10/replicate) are as follows:

Test Substance Loading Rate (mg/L)	Immobilization (%)* 24 hr	48 hr
0 (control)	0	0
46	0	0
99	3	7
210	27	57
460	100	100
1000	100	100

*mean of 3 replicates

Test condition : A 48 hour static toxicity test was carried out without renewal of the test solutions. Quantities of stock solutions of di-isopropyl ether in acetone were added in triplicate sets of 110 mL glass flasks so that when made up with reconstituted freshwater, an approximately logarithmic series of concentrations ranging from 46 to 1000 mg/L was produced. Three flasks served as controls and received no test substance. The concentration of acetone in all control and test flasks was 0.1 mL/L. Precautions were taken to (a) minimise evaporative loss of the test substance by use of glass cover slips over the vessel necks and (b) to minimize the risk of organisms becoming trapped at the surface by placing black paper caps over the flasks to create a darkened zone which the organisms would avoid.
The test temperatures were in the range 20 ± 2°C, pH was in the range 8.2 to 8.4, the total hardness was 164 mg/L as CaCO3, and dissolved oxygen was in the range 8.2 to 9.2 mg/L.
The daphnids were cultured in-house, derived from a strain obtained (via ICI Brixham Laboratory) from Institut National de Recherche Chimique Applique (I.R.Ch.A.), France. Age was <24 hours old from 15 to 35 day old parents.
All concentrations of test substance are expressed in terms of quantities initially added to the test vessels.

Conclusion : After Daphnia magna were exposed to test solutions of di-isopropyl ether for 48 hours in a static test, the 24 h and 48 h EC50 values were calculated to be 240 mg/L and 190 mg/L, respectively.

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because it did not analytically verify exposure concentrations and the results are based on nominal values.

Reference Number (24)

Type : Calculation
Species : *Daphnia* (no species)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 221.9
Method : other: ECOSAR version 0.99h, US EPA
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : ECOSAR version 0.99h, US EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound.

To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution

Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.

Result : EC50, 48 h, for Daphnia = 221.9 mg/L

Test condition : Experimental water solubility, 8800 mg/l @ 20°C (Heitmann, W et al, 1987), log Kow, 1.52 (Funasaki, N et al, 1985) and melting point, -86.6°C (SRC PhysProp database) were entered into the program.
Class: Neutral organics

Conclusion : The predicted 48 h LC50 value for Daphnia (221.9 mg/L) is in close agreement with the experimental 48 h EC50 value for Daphnia (190.0 mg/L) (Stephenson R.R., Shell Research Limited, Report No. SBGR.83.215).

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.

Reference Number (5)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Type : Calculation
Species : Green Alga (not specified)
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 134.9
ChV : = 10.2
Method : other: ECOSAR version 0.99h, US EPA
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : ECOSAR version 0.99h, US EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound.

To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.

Result : EC50, 96 h, for green algae = 134.9 mg/L
ChV, 96 h, for green algae = 10.2 mg/L

Test condition : Experimental water solubility, 8800 mg/l @ 20°C (Heitmann, W et al, 1987), log Kow, 1.52 (Funasaki, N et al, 1985) and melting point, -86.6°C (SRC PhysProp database) were entered into the program.

Class: Neutral organics

Conclusion : The predicted 96 h EC50 value for algae (134.9 mg/L) is in the same range as the predicted 48 h LC50 value for Daphnia (221.9 mg/L) and the predicted 96 h LC50 value for fish (214.1 mg/L). There is also good comparison between the predicted and experimental EC50 values for Daphnia (221.9 mg/l v 190.0 mg/L, respectively) and for fish (214.1 mg/l v 91.7 mg/L, respectively).

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.

Reference Number (5)

Type : Biomass
Species : *Selenastrum capricornutum* (alga, fresh water ATCC 22662)
Exposure period : 96 hour(s)
Unit : mg/L
EC50 : = >1000 mg/L
Analytical monitoring : no
Method : other: algae growth inhibition
Year : 1983
GLP : no data
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : A 4 d algal growth study was carried out using 10 concentrations of the test substance and a control. The test design included six control replicates and single vessels dosed with different concentrations of the test substance. 250-mL glass Erlenmeyer flasks served as the test vessels and held 50 mL of culture medium. Culture medium was prepare following the recipe given by Miller and Green (1978) with the following exceptions; 1) boric acid concentration = 105 μg/L, and 2) sodium bicarbonate concentration = 50 mg/L.

To 10 flasks, quantities of a test substance stock solution made up in acetone were added to give a logarithmic series of concentrations ranging from 1 to 1000 mg/L (1.0, 2.2, 4.6, 10, 22, 46, 100, 220, 460, and 1000 mg/L). The concentration of acetone in all flasks including controls was adjusted to 0.1 mL/L. Each flask was inoculated with *S. capricornutum* to give an initial cell density of 5×10^2 cells/mL. The algal inoculum was prepared from an actively growing liquid culture of *S. capricornutum* in exponential growth phase.

Flasks were incubated in a temperature controlled orbital incubator under constant illumination (approximately 3000 lux) at 24±2°C for 4 days. Cell counts were made on days 2 and 4 using an electronic particle counter (Coulter counter). The temperature in the incubator was measured at 4-h intervals. The pH of the control and highest test concentration was measured on days 0, 2, and 4. Temperature remained within the 24±2°C specified range, and the pH ranged from 8.3 to 8.5 in the measured vessels.

All determination of EC50 values were based on nominal test concentrations and cell counts.

Result : 96-hour EC50 = >1000 mg/L based on nominal concentrations.

The 96-hour cell counts in the treated flasks as a percent of the mean control cell counts were:

1.0 mg/L = 84%	46 mg/L = 127%
2.2 mg/L = 108%	100 mg/L = 130%
4.6 mg/L = 91%	220 mg/L = 113%
10 mg/L = 122%	460 mg/L = 127%
22 mg/L = 129%	1000 mg/L = 91%

Conclusion : 96-hour EC50 = >1000 mg/L based on nominal concentrations.
Reliability : (3) not reliable

Test concentrations were not measured and there is no indication in the report whether the test vessels were sealed. The reported LC_{50} value may reflect a loss of test substance by volatilization if the flasks were not tightly sealed.

Reference Number (24)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Vehicle	:	other: None; administered undiluted
Method	:	other: Similar to OECD 401
GLP	:	no
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Method	:	Administered orally to nonfasted rats. LD50 calculated by the method of Litchfield and Wilcoxon [1949]. Similar to OECD 401.
Remark	:	Test type: Acute oral toxicity Year: Prior to 1971 No. of animals/dose: 6 male for young adult and older adult 6 - 12 male and female for 14-day old rats Route of administration: Oral gavage Dose level: Variable Dose volume: Variable Control group included: No, but none needed
Result	:	14-day old: LD50 6.4 ml/kg [approx 4.5 g/kg] young adults: LD50 16.5 ml/kg [approx 11.6 g/kg] Older adults: LD50 16.0 ml/kg [approx 11.2 g/kg] G/kg dose based on a density of 0.72 g/ml
Test condition	:	Rats were observed for up to 7 days after dosing.
Test substance	:	Diisopropyl ether (CAS No. 108-20-3) Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Source/purity of test material is not specified, but stated to be analytical grade meeting ACS specifications.
Conclusion	:	DIPE, when administered to adult male Sprague-Dawley rats, had an acute oral LD50 of >10 g/kg. 14-day immature rats were considerable more sensitive [LD50 4.5 g/kg].
Reliability	:	(2) valid with restrictions Not GLP but conducted at a reputable laboratory [Abbot Laboratories, Chicago].
Reference Number		(13)

Species	:	rabbit
Strain	:	New Zealand white
Sex	:	no data
Number of animals	:	6
Vehicle	:	other: none reported
Doses	:	8.2, 7.2, 6.0, 5.2, 3.3, 1.62 g/kg
Method	:	other: Similar to OECD 401
GLP	:	no
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: Acute oral toxicity Year: Prior to 1939 Route of administration: Oral Dose levels: 8.2, 7.2, 6.0, 5.2, 3.3, 1.62 g/kg Dose volume: Variable Control: No - none needed
Result	:	Minimal lethal dose between 7 - 9 ml/kg

The symptoms noted were lack of coordination and unsteadiness at onset followed by a slight narcosis. In the animals that died the narcosis progressed towards a deep narcosis with loss of corneal reflex and evidences of depressant action on the medulla appeared, respiration became progressively slower, irregular and variable in amplitude and drop in body temperature till respiration failed. In the surviving animals, no effect on HB, erythrocyte count, total and differential leukocyte count was observed. No delayed toxicity was observed during the recovery period of 4 months after treatment.

Test substance : Diisopropyl ether (CAS No. 108-20-3)
Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '-
Test material is stated to be commercial grade with 3% of isopropyl alcohol, but with no peroxide nor added inhibitor.

Conclusion : The test article, when administered orally as received to New Zealand white rabbits had a minimal lethal dose of 7 - 9 ml/kg [approx 5 - 6.5 g/kg].

Reliability : (2) valid with restrictions
Not conducted by GLP but at a reputable laboratory [Kettering Laboratory, University of Cincinnati].

Reference Number (15)

5.1.2 ACUTE INHALATION TOXICITY

Species : guinea pig
Strain : other: not specified
Sex : no data
Vehicle : other: none
Doses : 0.3%; 1%; 3%; 6% in air
Method : other: not specified
GLP : no
Test substance : Diisopropyl ether (CAS No. 108-20-3)
Remark : Test type: Acute inhalation toxicity
Year: Prior to 1939
No. animlas/sex/group: One to two animals per dose
Route of administration: Inhalation
Dose level: 0.3%; 1%; 3%; 6% in air
Dose volume: N/A
Control: No
Result : 0.3 % (~3000 ppm)- 2 h: No visible indication of anesthetic action
1 and 3.0 % (~30000 ppm)- 1 h: Not lethal; signs of anesthesia
6.0% (~60000 ppm) : Death as the result of respiratory failure within 1 hr
Test condition : 1 or 2 hrs or until death [6%]
Test substance : Diisopropyl ether (CAS No. 108-20-3)
Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '-
Test material is stated to be commercial grade with 3% of isopropyl alcohol, but with no peroxide or added inhibitor.
Conclusion : The lowest lethal dose for 1 hr exposure was greater than 30,000 ppm in three species.
Reliability : (2) valid with restrictions
Not conducted by GLP. Few animals per group, but at a reputable laboratory [Kettering Laboratory, University of Cincinnati].
Reference Number (15)

Species : rabbit
Strain : New Zealand white
Sex : no data
Vehicle : other: none
Doses : 0.3%; 1%; 3%; 6% in air

Method	:	other: not specified
GLP	:	no
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: Acute inhalation toxicity Year: Prior to 1939 No. animlas/sex/group: One to two animals per dose Route of administration: Inhalation Dose level: 0.3%; 1%; 3%; 6% in air Dose volume: N/A Control: No
Result	:	0.3 % (~3000 ppm)- 2 h: No visible indication of anesthetic action 1 and 3.0 % (~30000 ppm)- 1 h: Not lethal; signs of anesthesia 6.0% (~60000 ppm) : Death as the result of respiratory failure within 1 hr
Test condition	:	1 or 2 hrs or until death [6%]
Test substance	:	Diisopropyl ether (CAS No. 108-20-3) Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Test material is stated to be commercial grade with 3% of isopropyl alcohol, but with no peroxide or added inhibitor.
Conclusion	:	The lowest lethal dose for 1 hr exposure was greater than 30,000 ppm in three species.
Reliability	:	(2) valid with restrictions Not conducted by GLP. Few animals per group, but at a reputable laboratory [Kettering Laboratory, University of Cincinnati].
Reference Number		(15)

Species	:	monkey
Strain	:	other: Macacus rhesus
Sex	:	female
Vehicle	:	other: none
Doses	:	0.3%; 1%; 3%; 6% in air
Method	:	other: not specified
GLP	:	no
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: Acute inhalation toxicity Year: Prior to 1939 No. animlas/sex/group: One to two animals per dose Route of administration: Inhalation Dose level: 0.3%; 1%; 3%; 6% in air Dose volume: N/A Control: No
Result	:	0.3 % (~3000 ppm)- 2 h: No visible indication of anesthetic action 1 and 3.0 % (~30000 ppm)- 1 h: Not lethal; signs of anesthesia 6.0% (~60000 ppm) : Death as the result of respiratory failure within 1 hr
Test condition	:	1 or 2 hrs or until death [6%]
Test substance	:	Diisopropyl ether (CAS No. 108-20-3) Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Test material is stated to be commercial grade with 3% of isopropyl alcohol, but with no peroxide or added inhibitor.
Conclusion	:	The lowest lethal dose for 1 hr exposure was greater than 30,000 ppm in three species.
Reliability	:	(2) valid with restrictions Not conducted by GLP. Few animals per group, but at a reputable laboratory [Kettering Laboratory, University of Cincinnati].
Reference Number		(15)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50

Species	:	rabbit
Strain	:	New Zealand white
Sex	:	no data
Vehicle	:	other: none
Doses	:	variable
Method	:	other: Similar to OECD 402
GLP	:	no
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: Acute dermal toxicity Year: Prior to 1939 No. of animals/sex/group: Unspecified Route of administration: Dermal Dose level: variable Control: No
Result	:	No deaths or systemic effects were reported. In rabbits dermal unoccluded LD50 > 2.0 g/kg. The actual dose applied was much higher, but continued to evaporate from the skin during application.
Test condition	:	The material was continuously dripped onto the shaved skin to keep it wet for one hour, while continuously evaporating. 150 ml of material was used.
Test substance	:	Diisopropyl ether (CAS No. 108-20-3) Chemical Name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Test material is stated to be commercial grade with 3% of isopropyl alcohol, but with no peroxide or added inhibitor.
Conclusion	:	The test article, when administered dermally to New Zealand white rabbits had an acute dermal LD50 of greater than 2.0 g/kg.
Reliability	:	(2) valid with restrictions Not GLP but conducted at a reputable laboratory [Kettering Laboratory, University of Cincinnati].
Reference Number		(15)

5.3 SENSITIZATION

Type	:	other: In vitro chemical reactivity assay, surrogate for respiratory sensitization
Species	:	other: No animals; in vitro chemical assay
Number of animals	:	0
Vehicle	:	other: None
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other: No guideline available
Year	:	1990
GLP	:	no
Test substance	:	Diisopropyl ether (CAS No.108-20-3)
Remark	:	Route of administration: N/A Sex: N/A Dose level: N/A Dose volume: N/A Control group included: Positive and negative controls included
Result	:	Diisopropanol was negative in this in vitro assay for potential respiratory sensitization. The assay gave positive responses with several known respiratory sensitizers.
Test condition	:	A method for monitoring chemical reactivity in aqueous solutions, at neutral pH and 37 degrees C, was developed. The chemical was allowed to react with a lysine-containing peptide, and the reaction was monitored with high-performance liquid chromatography. Simple acids, bases, and solvents did not react with the peptide, whereas isocyanates, anhydrides, and chloramine-T, substances well known for their sensitizing and asthma inducing properties, did. Thus a positive test strongly suggested that the

chemical had the potential to act as a hapten and cause sensitization when inhaled.

Test substance : Diisopropyl ether (CAS No.108-20-3)
Chemical Name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '-
Source/purity not specified.

Conclusion : Di-isopropanol was negative in this in vitro assay.

Reliability : (2) valid with restrictions
Not conducted by GLP; research method not accepted by regulatory agencies; in vitro surrogate for respiratory sensitisation.

Reference Number (26)

5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 6 hours/day
Frequency of treatm. : 5 days/week for ~13 weeks
Doses : 0, 480, 3300, or 7100 ppm
Control group : other: yes (untreated & sham-exposed)
NOAEL : = 480 ppm
Method : EPA OTS 798.2450
Year : 1996
GLP : no data
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : Statistical method:
Statistical analyses of numerical data included ANOVA and Tukey's studentized range test for data on serum chemistry. Duncan's multiple range test was used for hematology and body weights to assess statistically significant differences between control and exposed groups.

Remark : Male and female rats were acclimated for 2 weeks before initiation of exposures that began at ~8 weeks of age. Exposed animals were individually housed in 1-m3 inhalation chambers. Untreated control animals were housed in a separate room in identical caging. Room environment was set to 20-22ºC and 40-60% relative humidity. Lights were on a 12/12-hr light/dark cycle. Food and water were provided ad libitum except during exposures.

Vapors were generated by metering DIPE on to a warmed fiberglass wick and carried to the three 1m3 exposure chambers by a stream of measured and filtered room air. Temperature and humidity in the chambers were measured every 30 minutes and air flow through each chamber was metered to provide at least 12 air changes/hour. Chamber air samples were collected with a gas-tight syringe and analyzed with a gas chromatograph with a flame ionization detector and a fused silica column. Samples were periodically obtained for analysis by gas chromatography/ mass spectroscopy.

The primary endpoints during the course of exposures were individual body weights recorded weekly and clinical signs recorded daily except on weekends.

Following the last exposure, rats were fasted overnight and weighed; blood samples were obtained via the orbital sinus using light anesthesia. Samples were used to determine values for WBC, RBC, Hgb, Hct, MCV, MCH, MCHC, platelets, and differential counts. Glucose, urea nitrogen, total protein, albumin, globulin, A/G ratio, sorbitol dehydrogenase,

aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, creatinine, cholesterol, triglycerides, uric acid, Cl, Ca, Na, K, and P. Following the collection of blood samples, all animals were euthanized with sodium pentobarbital (i.p.) and exanguinated. Approximately 40 tissues were collected for histopathology and organs were weighed. Testis and associated tissues were preserved whole in 10% buffered formalin except for the left cauda epididymis of 10 rats in both control groups and the highest test group; epididymides were evaluated for morphology and number of sperm. The left testis in these groups was weighed and used for determination of number of testicular spermatids.

Type: 90-Day Subchronic
Species/strain: Rat/Sprague-Dawley; Tac:N(SD)fBR
No./sex/dose: 14/sex/group
Vehicle: None
Method: USEPA 1984, 40CFR Part 798:2450

Result : DIPE did not adversely affect clinical signs body weight, serum chemistry, hematology, or the number of sperm or spermatids. Exposure to males at 7100 ppm resulted in hypertrophy of liver cells associated with increased liver weight and in increased kidney weight with an increased incidence of hyaline droplets in proximal tubules of the kidney. Females had increased weight of both liver and kidney, although kidney increased only in relation to sham-exposed controls and no morphologic changes were observed in either organ. At 3300 ppm, weights of liver and kidney were increased in males; the liver weights were increased in females only compared to sham-exposed controls and not untreated controls. No morphologic abnormalities were observed. No changes were observed with 480 ppm.

Test substance : Diisopropyl Ether (CAS No. 108-20-3); purity ~92%.

Conclusion : NOAEL = 480 ppm

Reliability : (2) valid with restrictions
GLP unknown. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Reference Number (3)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 6 hours/day
Frequency of treatm. : 5 days/week for ~13 weeks
Doses : 0, 450, 3250, or 7060 ppm
Control group : other: yes (sham-exposed)
Method : other: USEPA 1984, 40CFR Part 798:6050, 6400, and 6200
Year : 1997
GLP : no data
Test substance : Diisopropyl Ether (CAS No. 108-20-3)
Method : Statistical method:
All statistical analyses were performed with SAS software. Body weights, rectal temperatures fore- and hindlimb grip strengths, the number of rears, and motor activity were analyzed by a one-way analysis of variance followed by Duncan's multiple range test. The remaining data from the FOB were analyzed by Fisher's exact test using an extended contingency table containing all four groups of at given sex at a specified time. If a significant difference occurred for a given parameter, Fisher's exact test was used to directly compare each group individually against the control. Brain weights, lengths and widths, were analyzed by Student's t-test.

Remark : Male and female rats were acclimated for 2 weeks before initiation of exposures that began at ~8 weeks of age. Sham-exposed and exposed animals were individually housed in 1-m3 inhalation chambers except during behavioral testing, when they were placed in another room overnight

and evaluated the following day. Room environment was set to 20-22ºC and 40-60% relative humidity. Lights were on a 12/12-hr light/dark cycle. Food and water were provided ad libitum except during exposures. Exposure vapors were generated by metering DIPE on to a warmed fiberglass wick and carried to the three 1-m3 exposure chambers by a stream of measured and filtered room air. Temperature and humidity in the chambers were measured every 30 minutes and air flow through each chamber was metered to provide at least 12 air changes/hour. Chamber air samples were collected with a gas-tight syringe and analyzed with a gas chromatograph with a flame ionization detector and a fused silica column. Samples were periodically obtained for analysis by gas chromatography/ mass spectroscopy.

Exposures were stagger-started over a 5-day period with 16 animals, 2/sex/group, receiving their first exposure on each of 5 consecutive days.

The rats were observed for signs of toxicity daily prior to initiation of exposures, and individual body weights were recorded weekly.

During weeks of Functional Observation Battery (FOB) evaluation, four rats/group would be removed from the inhalation chamber and housed separately overnight and evaluated on the following day between the hours of 7:30 a.m. and 11:00 a.m. The process was repeated for each consecutive day until all rats were evaluated. The rats were evaluated with minimal disruption to the exposure schedule and with a manageable number of rats per day, 16 on any given day. The animals were evaluated in an FOB followed by a determination of motor activity prior to initiation of exposure; the FOB following 2, 4, 8, and 13 weeks of exposures, and for motor activity following 4, 8, and 13 weeks of exposures. Following the final determination of motor activity, the animals were anesthetized, intravascularly perfused, and the brain, spinal cord, and peripheral nerves removed for microscopic examination.

The FOB consisted of initially observing home-cage positioning, posture, and reaction to removal from the cage. This was followed by evaluation for exophthalmus/palpebral closure, lacrimation, salivation, pupillary response, palpebral reflex, and pinna reflex. These observations were scored by type and intensity. The animals were then observed for open field behavior. Piloerection, respiratory rate, tremors, convulsions, posture, gait, ataxic gait, tail elevation, unperturbed activity level, vocalization, number of rears, fecal balls, and urine pools were all recorded during the open-field observations. Reactions to the approach of a pencil, finger snap, and tail pinch were ranked and recorded. Finally, fore- and hindlimb grip strength , rectal temperature , and body weight were measured. Automated motor activity was assessed for 30 minutes in figure-eight mazes after the completion of the FOB.

Following the last FOB and motor activity evaluation, the rats were anesthetized with heparinized sodium pentobarbital (i.p.). The thoracic cavity was opened and the animals were infused with phosphate-buffered gluteraldehyde through the left ventricle. The perfused brain, spinal cord, and sciatic nerve with its tibial, sural, and peroneal divisions were removed. The brain and nerve tissues were processed for embedding in paraffin or glycol methacrylate (dorsal root ganglia and peripheral nerves) and sectioned for light or electron microscopic pathologic evaluation.

Type: 90-Day Neurotoxicity
Species/strain: Rat/Sprague-Dawley; Tac:N(SD)fBR
No./sex/dose: 10/sex/group
Vehicle: None
Method: USEPA 1984, 40CFR Part 798:6050, 6400, and 6200

Result **:** Motor activity in a figure-eight maze and unperturbed activity in the FOB

were decreased at week 4 in females exposed to 7060 ppm; activity in the FOB was also decreased in females exposed to 450 ppm at week 4. Other changes in the FOB appeared to be minor, and no changes were observed during microscopic examination of tissues from the nervous system.

Test substance : Diisopropyl Ether (CAS No. 108-20-3); purity ~92%.

Conclusion : Inhalation exposures to DIPE at concentrations as high as 7060 ppm for 13 weeks resulted in few observable effects on the nervous system.

Reliability : (2) valid with restrictions
GLP unknown. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Reference Number (21)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse mutation assay

System of testing : Salmonella typhimurium

Test concentration : Up to 8000 ug/ml in the pre-incubation mix

Metabolic activation : with and without

Result : negative

Method : other: Similar to OECD Guideline 471

Year : 1988

GLP : no data

Test substance : Diisopropyl ether (CAS No. 108-20-3)

Remark : Strains tested: Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, TA1538

Exposure method: Preincubation assay for volatile compounds [Brooks and Dean 1981]

Test Substance Doses/concentration levels: Up to 8000 ug/ml in the pre-incubation mix

Metabolic activation: With and without (S9 fraction mix of livers of Aroclor 1254 pretreated rats)

Vehicle: Tween 80/ethanol

Tester strain, activation status, Positive Controls and concentration level: Not stated

Statistical analysis: Mean revertant colony count and standard deviation were determined for each dose point.

Dose Rangefinding Study: Cytotoxicity study

S9 Optimization Study: No

Result : DIPE did not induce reverse gene mutation in any strain. The test substance was not genotoxic in this assay with or without metabolic activation.

Test substance : Diisopropyl ether (CAS No. 108-20-3)
Chemical Name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '-
Source/purity not specified.

Conclusion : Under the conditions of this study, the test material was not mutagenic.

Reliability : (2) valid with restrictions
Restriction due to the lack of any information regarding the selection of dose levels used during the study. In addition no information is presented regarding cytotoxicity or the presence of test material precipitate in the cultures. Although study was not stated to be conducted under GLP, it was conducted at a reputable laboratory [Shell Research Limited, Sittingbourne

Research Center].

Reference Number (2)

Type	:	Sister chromatid exchange assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	Up to 1200 ug/ml
Metabolic activation	:	without
Result	:	negative
Method	:	other: Similar to OECD Guideline 473
Year	:	1984
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: Chromosome damage Exposure method: For volatile compounds Metabolic activation: Metabolic activation S9 was not added because liver cells are metabolically competent Vehicle: Tween 80/ethanol Tester strain, activation status, Positive Controls and concentration level: Cultured CHO cells were grown in 80 cm2 flasks for 24 hr before compound treatment. Treatment periods were 5 hr in the presence of S9 mix and 24 hr in the absence of S9. Colcemid was added to all cultures 22 hr after the initial treatment. After a further 2 hr, the cells were trypsinized, resuspended in hypotonic solution and then fixed, before spotting onto slides. Cell preparations were then stained with Giemsa. The slides were randomly coded and 100 cells from each culture were analyzed microscopically. Mitotic index estimations were also made. The positive controls were ethylmethanesulfonate [-S9] and cyclophosphamide [+S9]. Vehicle control: Yes Dose rangefinding study: Cytotoxicity study S9 Optimization study: No
Result	:	DIPE did not induce chromosomal damage in CHO cells. The test substance was not genotoxic in this assay.
Test substance	:	Di-isopropyl ether (CAS No. 108-20-3) Chemical Name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Source/purity of test material: 98.5%
Conclusion	:	Under the conditions of this study, the test material was not mutagenic.
Reliability	:	(2) valid with restrictions Restriction due to the lack of any information regarding the selection of dose levels used during the study. In addition no information is presented regarding cytotoxicity or the presence of test material precipitate in the cultures. Although study was not stated to be conducted under GLP, it was conducted at a reputable laboratory [Shell Research Limited, Sittingbourne Research Center].

Reference Number (2)

Type	:	DNA damage and repair assay
System of testing	:	Rat liver cells
Test concentration	:	Up to 1200 ug/ml
Metabolic activation	:	without
Result	:	negative
Method	:	other: Similar to OECD Guideline 476
Year	:	1984
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)

Remark	:	Test type: Chromosome damage Strains tested: RL4 Metabolic activation: Metabolic activation S9 was not added because liver cells are metabolically competent. Vehicle: Tween 80/ethanol Tester strain, activation status, Positive Controls and concentration level: Cultured rat liver cells were grown and treated on glass microscope slides contained in 100 ml glass Leighton tubes. After 22 hr exposure to test compound or solvent, colcemid was added to each culture. After a further 2 hr, the slides were removed, subjected to hypotonic treatment followed by fixation and stained with Giemsa. The preparations were randomly coded and 100 cells from each culture were analyzed microscopically. The positive control was 7,12-dimethylbenzanthracenene. Vehicle control: Yes Dose rangefinding study: Cytotoxicity study S9 Optimization study: None needed
Result	:	DIPE did not induce chromosomal damage in rat liver cells. The test substance was not genotoxic in this assay.
Test substance	:	Di-isopropyl ether (CAS No. 108-20-3) Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Source/purity of test material: 98.5%
Conclusion	:	Under the conditions of this study, the test material was not mutagenic.
Reliability	:	(2) valid with restrictions Restriction due to the lack of any information regarding the selection of dose levels used during the study. In addition no information is presented regarding cytotoxicity or the presence of test material precipitate in the cultures. Although study was not stated to be conducted under GLP, it was conducted at a reputable laboratory [Shell Research Limited, Sittingbourne Research Center].
Reference Number		(2)

Type	:	Gene mutation in Saccharomyces cerevisiae
System of testing	:	Saccharomyces cerevisiae
Test concentration	:	Up to 8000 ug/ml in the pre-incubation mix
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Similar to OECD Guideline 481
Year	:	1984
GLP	:	no data
Test substance	:	Diisopropyl ether (CAS No. 108-20-3)
Remark	:	Test type: Yeast mitotic gene conversion Strains tested: JD1 Exposure method: [Brooks and Dean 1981] Metabolic activation: With and without (S9 fraction mix of livers of Aroclor 1254 pretreated rats) Vehicle: Tween 80/ethanol Tester strain, activation status, Positive Controls and concentration level: Yeast cells were grown in log-phase, washed and resuspended in 2/5 strength YEPD broth at a concentration of 1 X 107 cells/ml. The

suspension was divided into 1.9 ml amounts in 30 ml universal containers and 0.1 ml of test compound solution was added. For experiments with metabolic activation [+S9], 0.1 ml of DIPE was added to0 1.6 ml of yeast cell suspension, together with 0.3 ml of S9 mix. Initially a range of concentrations of DIPE was tested up to 5 mg/ml if solubility allowed. A second experiment was performed based on these results and taking into account cell viability. The cultures were incubated with shaking at 30 C for 18 hr. Aliquots were plated onto the appropriate culture media for selection of mitotic gene convertants and cells surviving the treatment. Mitotic gene conversion may be scored by supplementing the minimal medium with histidine to score tryptophan prototrophs, and with tryptophan to score histidine prototrophs. Control plates were set up with solvent alone and with the positive control compounds 4-nitroquinoline oxide and cyclophosphamide.

Vehicle control: Yes

Dose rangefinding study: Cytotoxicity study

S9 Optimization study: No

Result	:	DIPE did not induce mitotic gene conversion I yeast. The test substance was not genotoxic in this assay with or without metabolic activation.
Test substance	:	Di-isopropyl ether (CAS No. 108-20-3) Chemical name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '- Source/purity of test material: 98.5%
Conclusion	:	Under the conditions of this study, the test material was not genotoxic.
Reliability	:	(2) valid with restrictions Restriction due to the lack of any information regarding the selection of dose levels used during the study. In addition no information is presented regarding cytotoxicity or the presence of test material precipitate in the cultures. Although study was not stated to be conducted under GLP, it was conducted at a reputable laboratory [Shell Research Limited, Sittingbourne Research Center].
Reference Number		(2)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hr/day
Frequency of treatm.	:	Gestation Days 6-15
Duration of test	:	20 days
Doses	:	0, 430, 3095, or 6745 ppm
Control group	:	other: yes (untreated & sham-exposed)
other: NOEL Maternal	:	= 430 ppm
other: NOEL Pup	:	= 430 - ppm
Result	:	Maternal NOEL: 430 ppm; Pup NOEL: 430 ppm
Method	:	EPA OTS 798.4350
Year	:	1996
GLP	:	no data
Test substance	:	Diisopropyl Ether (CAS No. 108-20-3)
Method	:	Statistical method: Statistical analyses of numerical data included ANOVA and Tukey's studentized range test for data on serum chemistry. Duncan's multiple range test was used for hematology and body weights to assess statistically significant differences between control and exposed groups.

Data on the maternal biophase, cesarean sections, and fetuses were evaluated by ANOVA followed by group comparisons using Fisher's exact or Dunnett's test.

Remark : Nulliparous females were housed with males in a 1:1 ratio and observed daily for evidence of breeding activity. Females positive for sperm plug and for sperm in the vaginal lavage fluid were considered to be at day 0 of gestation and were individually housed. The females were then randomly distributed to 5 groups of 22 animals each: untreated controls, sham-exposed controls, and 3 groups exposed to vapors of DIDP at 430, 3095, or 6745 ppm for 6 hr/day on gestation days (GD) 6-15.

Vapors were generated by metering DIPE on to a warmed fiberglass wick and carried to the three 1m3 exposure chambers by a stream of measured and filtered room air. Temperature and humidity in the chambers were measured every 30 minutes and air flow through each chamber was metered to provide at least 12 air changes/hour. Chamber air samples were collected with a gas-tight syringe and analyzed with a gas chromatograph with a flame ionization detector and a fused silica column. Samples were periodically obtained for analysis by gas chromatography/ mass spectroscopy.

Sham-exposed and test animals were housed in their exposure chambers throughout the exposure period; untreated controls in a separate room. Food and water were not available during the 6 -hour exposure periods but were available ad libitum at all other times. All animals were observed daily. Body weights were recorded on days 0, 6, 13, 16, and 20. Food consumption was measured on GD 6, 13, 16, and 20. Females were sacrificed on GD 20 by diethyl ether overexposure followed by exsanguination. Serum samples from the descending aorta were analyzed for glucose, urea nitrogen, total protein, albumin, globulin, A/G ratio, sorbitol dehydrogenase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, creatinine, cholesterol, triglycerides, uric acid, Cl, Ca, Na, K, and P. All organs were examined grossly. The number of corpora lutea per ovary and the gravid uterine weights were recorded. Uterine contents were examined and the numbers of implantation sites, early and late resorptions, and live and dead fetuses were recorded. The gender of each fetus was recorded. Fetuses were weighed and examined for gross anomalies. Fetuses of each litter were equally distributed between two groups; half were fixed in Bouin's solution and examined for visceral anomalies and the remaining fetuses were fixed in 95% ethanol and examined for skeletal anomalies after differential staining for cartilage and bone.

Dams exposed to 6745 ppm had a slight reduction in body weight gain and a significant decrease in food consumption. A concentration-related increase in the incidence of rudimentary 14th ribs was observed (statistically significant at 3095 and 6745 ppm) but the relevance of the finding was uncertain. There was no apparent toxicity, either maternal or fetal, at the lowest exposure concentration, 430 ppm.

Type: Developmental Toxicity
Species/strain: Sprague-Dawley; VAF/Plus Crl:CD(SD)BR
No./dose: 22/group
Vehicle: None
Method: USEPA 1984; 40CFR Part 798:4350

Result : Maternal NOEL: 430 ppm
Pup NOEL: 430 ppm

Test substance : Diisopropyl Ether (CAS No. 108-20-3); purity ~92%.

Conclusion : DIPE is not a teratogen.

Reliability : (2) valid with restrictions
GLP unknown. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Reference Number (3)

5.11 ADDITIONAL REMARKS

Type : other: Sensory Irritation in Humans
Method : Non-guideline.
Remark : Species/strain: Humans
Sex: Male and female
Number/sex/group: Average of 12
Route of administration: Inhalation
Vehicle: None
Control: No
Year: Prior to 1946
GLP: No
Result : 300 ppm: 35% of the subjects objected to this solvent because of the unpleasant odor rather than irritation.
500 ppm: there was a sensory response that was acceptable to the majority of subjects.
Test condition : Subjects were exposed for 15 minutes and olfactory fatigue and irritation of mucous membranes were reported. "Motion pictures were shown to occupy the subject's attention and divert their thoughts from the atmospheric contamination to which they were exposed."
Test substance : Diisopropyl ether (CAS No. 108-20-3)
Chemical Name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '-
Test material is stated to be technical grade product.
Conclusion : DIPE does not appear to be a sensory irritant at concentrations up to 500 ppm, but it does have an unpleasant odor at this concentration.
Reliability : (2) valid with restrictions
Not GLP but conducted at a reputable laboratory [Harvard School of Public Health, Boston].
Reference Number (23)

Type : other: Sensory irritation in humans
Method : Non-Guideline.
Remark : Species/strain: Young adult humans [University of California staff and medical students]
Sex: Not specified
Number/sex/group: Not specified
Route of administration: Inhalation
Vehicle: None
Control: No
Year: 1955
GLP: No
Result : Numbers of subjects with degree of effect
Concentration 400 ppm 800 ppm
Number subjects: 7 7
Eye irritation: 7 absent 3 absent, 3 slight, 1 mod.
Nose irritation: 5 absent, 2 slight 2 absent, 5 slight
Pulmonary discomfort: 7 absent 4 absent, 3 slight
Olfactory cognition : 1 slight, 6 mod. 4 mod., 3 severe
CNS effects : 7 absent 7 absent
Test condition : Exposures were conducted in a whole-body chamber approximately 7700 l equipped with a fan. Exposures were made in a static atmosphere generated by vaporizing a predetermined quantity of test solvent from a hot surface. Five minutes were allowed for evaporation and equilibration, and subjects were exposed for 5 minutes, during which time they noted the degree of subjective responses at one-minute intervals.
Test substance : Diisopropyl ether (CAS No. 108-20-3)

Chemical Name: Isopropyl ether; isopropoxy propane, 2-; oxybis [propane], 2,2 '-
Test material is stated to be commercial grade with purity of 98% or better, provided by Shell Chemical Corporation.

Conclusion : 400 ppm: 5 mins of inhalation exposure caused no eye irritation, none to slight nose irritation, no pulmonary discomfort, olfactory recognition but no central nervous system effects.

800 ppm: 5 mins of inhalation exposed caused slight eye and nose irritation, none to slight pulmonary discomfort, definite olfactory recognition but no central nervous system effects.

Reliability : (2) valid with restrictions
Not GLP but conducted at a reputable laboratory [University of California School of Medicine].

Reference Number (12)

(1) Bridié A, Wolff C and Winter M (1979). The acute toxicity of some petrochemicals to goldfish. Water Res. 13, 623-626.

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